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Preoperative Pulmonary Evaluation

As Viewed by the Internist

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• **The internist as well as the surgeon finds thorough pulmonary functional evaluation of the patient for operation an invaluable adjunct to strictly clinical judgment in two large categories of patients: Those with significant inconsistencies between clinical impression and functional analysis of pulmonary reserve as well as in those with borderline functional reserve where operation is imperative.**

PREOPERATIVE PULMONARY EVALUATION for appraisal of surgical risk may require more careful analysis than a clinical impression. It need hardly be mentioned that evaluation of the patient for elective operation is quite different from evaluation for emergency intervention. In emergency, time is a factor that cannot be neglected. The preoperative revelations of a chest x-ray in addition to the stethoscope, the electrocardiographic contributions to auscultation of the heart, a urine examination, hematocrit determination and examination of a specimen of blood, blood grouping and determination of nonprotein nitrogen, sugar content and carbon dioxide combining power may be all one needs to be prepared to cope with most complications that may develop.

Emergency operations upon the thorax and the thoracic organs are rather uncommon except following severe trauma. Most emergency thoracic procedures come at a time when function has already been seriously impaired and operation must be expected to improve rather than diminish function further. This is true in patients with ruptured emphysematous blebs and tension pneumothorax; it is true in cases of chest trauma, in patients with rupture of the esophagus; and it is true even when operation is done to stop bleeding. In such cases the patient has already survived a severe trial of pulmonary insufficiency and in these situations operation can be performed even if objectively evaluated pulmonary reserve proves to be well below the acceptable minimum of reserve ordinarily required for transthoracic operation.

This communication is concerned with pulmonary evaluation for elective operations, principally to screen out patients unfit for operation because of pulmonary insufficiency. It should be clearly stated, however, that this evaluation of pulmonary reserve reflects the thoughts of an internist and chest physician, not those of a pulmonary physiologist. Its purpose is to depict the clinical usefulness of the findings of the pulmonary function laboratory. The de-

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tailed pulmonary function studies in the cases here reported upon were done under the direction of Dr. Edward A. Gaensler with his associates, Dr. Asher Marks, Dr. Inga Lindgren, Dr. John B. Cadigan, Jr. and formerly Dr. David W. Cugell, in the Pulmonary Physiology Laboratories of the Boston Sanatorium and the Boston City Hospital. The usefulness of these studies to the internist, in his evaluation of surgical risk, is the purpose of this paper.

Clinical evaluation is an inseparable component of preoperative evaluation but objective physiologic studies have come to play an increasingly important part in one's judgment of pulmonary reserve.

PRELIMINARY SCREENING

Many times when a thoracic operation is contemplated, elaborate lung function studies are neither available nor necessary. Initial screening tests for pulmonary reserve can be those of the clinician in the examining room of his office or the hospital. It should be a function of the pulmonary physiology laboratory to contribute to the diagnostic acumen and the facilities of the clinician by the adaptation of function tests for office use. Use of the fluoroscope, with its view of the dynamic action of the heart, the lungs and the thorax, should supplement the history of symptoms and the physical examination, for it can contribute considerable accuracy in the estimation of pulmonary reserve. A searching history and complete physical examination are background data for careful surgeons. It is not always possible historically, to separate the symptoms of primary pulmonary origin from those secondary to cardiac disease, so closely interdependent are these two systems. The following symptomatic information may be revealing:

1. *Signs and Symptoms of Pulmonary Origin:*
   - Breathlessness (1 or 2 flights)
   - Cough (character)
   - Sputum (amount and character)
   - Hemoptysis without pleurisy
   - Wheezing
   - Previous chest plates
   - Dyspnea without orthopnea
   - Known pulmonary disease
   - Previous chest surgery
   - Asthma and other allergies
   - Chest pain (character)
   - Occupation, familial pulmonary disease.
2. *Signs and Symptoms of Cardiovascular Origin:*
   - Known cardiac disease
   - Rheumatic state
   - Family or personal embolic history
   - Orthopnea, precordial pain with effort
   - Paroxysmal nocturnal dyspnea
   - Peripheral and sacral edema
   - Previous electrocardiograms
   - Fatigue and limitation of activity
   - Palpitation and irregularities of cardiac origin.

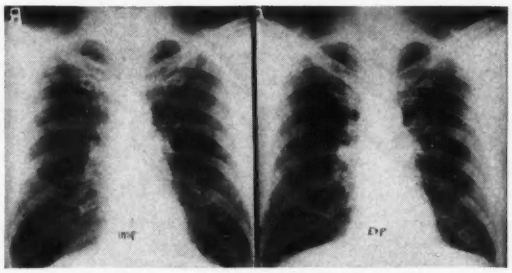

Figure 1 (Case 1).—*Left:* Inspiration. *Right:* Expiration, with diaphragms equivalent to 4.5 cm. higher than on inspiration, smoother and more rounded. Not shown was the very slow movement of 9.0 seconds by fluoroscopy to acquire this degree of elevation.

Specific factual data from pulmonary observations should be added to this historical framework. A stethoscope, the use of which is understood, a tape measure, a flight of stairs, a watch, a skin pencil and a few x-ray films of the chest will enable the clinician to screen out the pulmonary sufficient from the insufficient. As adjuncts to keen clinical observation, the fluoroscope and a timed vital capacity machine for measuring breathing performance in volume per unit of time are the two most useful pieces of screening apparatus for the office. Roentgenologists are not accustomed to report the type of information that is useful to the clinician for the determination of obstructive and restrictive defects in breathing. Fluoroscopy by the clinician should be reserved primarily for observing the dynamic action of the thoracic organs within the chest, as well as their silhouettes. The x-ray examination of the lungs should be relied on only for the detection and analysis of parenchymal disease. Definitive x-ray observations should complement fluoroscopy and the physical examination. The following observations which have proved most essential for preliminary screening and evaluation of lung function are based upon my personal experience with 350 fluoroscopic examinations in the office:

Fluoroscopic Screening for Lung Function

1. Chest wall—expansion in diagonal view, marked and measured on screen in centimeters.
2. Heart and vessels—position, silhouette, pulsations.
3. Diaphragms:
   (a) Position—at posterior ribs.
   (b) Equality or differences in action.
   (c) Maximum excursion—marked on screen and measured in centimeters.
   (d) Speed of excursion—fast or slow—but timed for maximal rise.
4. Lungs:
   (a) Comparative radiance.
   (b) Abnormal shadows—fluid—free air.
   (c) Trapping of air—unusual localized radiance at end of expiration and mediastinal motion.

The timed vital capacity machine devised by Gaensler[2] in our laboratories is a simple vital ca-

pacity machine with an electronic timing device for measuring the volume of air exhaled in the first, the first two or the first three seconds of the maximal expiratory effort in addition to the total vital capacity. Normal persons exhale 75 to 90 per cent of their total vital capacity in one second and 90 to 100 per cent in three seconds. Persons with obstructions to the flow of air out of the lungs may, for example, exhale only 25 to 60 per cent of their total vital capacity in the first second. On the contrary, persons with pulmonary fibrosis or other restrictive parenchymal lesions without airway obstruction and those with muscular weakness or paralysis or lack of "driving power" may have a reduced or restricted total vital capacity but may exhale a normal or greater than normal per cent of that volume in one second.

The following case is illustrative of the usefulness of these pulmonary screening examinations.

CASE 1. The patient was a 50-year-old administrator with a family history of four generations of severe shortness of breath consistent with emphysema. His own difficulties in breathing were of six years' duration, slowly and progressively becoming worse. He was a tall, well-built active man with dusky lips who was obviously short of breath at rest.

The results of office examination and functional evaluation were as follows:

Lungs: Hyper-resonant—clear—breath sounds faint.

Fluoroscopy: Chest expansion 1 cm.—radiant++.

Diaphragms: Twelfth rib—maximal excursion 4.5 cm. Paradoxical in motion at onset of inspiration and expiration—speed of expiration 9.0 seconds.

Heart: Small—pulmonary conus prominent

Vital Capacity: 4,200 cc., 100 per cent of predicted normal.

Timed Vital Capacity: 36 per cent of total vital capacity in 1 second.

Conclusion: Advanced pulmonary emphysema.

These findings, entirely consistent with advanced emphysema, were confirmed by more detailed study for specific problems of therapy.

The inspiratory and expiratory x-ray films of the chest (Figure 1) showed the low diaphragm with very little difference in the two positions. The x-ray silhouette showed a prominence of the pulmonary conus in the right anterior diagonal view, typical of cor pulmonale (Figure 2).

Thus, the history, the office examination, fluoroscopy and timed vital capacity gave a clear-cut picture of the severity of disease. Also illustrated was the well known fact that determination of the vital capacity alone is of little value. On the contrary, for preoperative evaluation, reliance on this "objective" test alone may lead to disastrous consequences. In this man with dyspnea at rest and far advanced emphysema, the vital capacity was 100 per cent of normal.

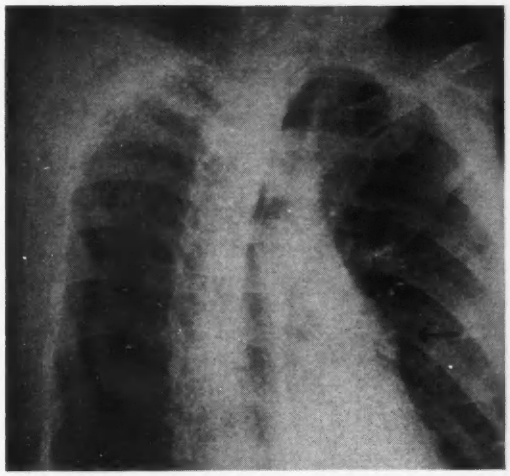

Figure 2 (Case 1).—Right anterior diagonal view of patient in Figure 1, showing considerable prominence of pulmonary conus, from increased pulmonary arterial pressure in advanced obstructive emphysema.

It is not necessary to explore all techniques of preoperative pulmonary evaluation beyond these preliminary office screening procedures, but there are specific indications for special and thorough investigation of pulmonary reserve,[9] as follows:

Indications for Special Function Studies

1. Inconsistencies between the clinical impression and screening functional analysis of pulmonary reserve.[3]
2. Dyspnea not explained by x-ray films or routine function studies.
3. Borderline functional reserve where operation is imperative, requiring differential bronchospirometry.[4]

Doubts or inconsistencies between the clinical impression of pulmonary reserve and preliminary screening functional tests should be a sound criterion for more elaborate and definitive studies of pulmonary function. The type of operation anticipated may be modified not only by the degree of pulmonary insufficiency but by the infringement of specific surgical procedures upon existing pulmonary reserve.[9]

Dyspnea not explained by the x-ray or preliminary screening studies is seen largely in patients with diffuse pulmonary lesions of varying severity as observed by x-ray, yet have essentially normal results of ventilatory studies. The process, widely disseminated in the alveolar membranes in certain granulomatous and fibrotic diseases of the lungs, is such as to effect the diffusion of gases in the so-called "alveolar-capillary block" syndrome described by Cournand.[1]

This complicated subject is not under discussion here, chiefly because such patients usually have dif-

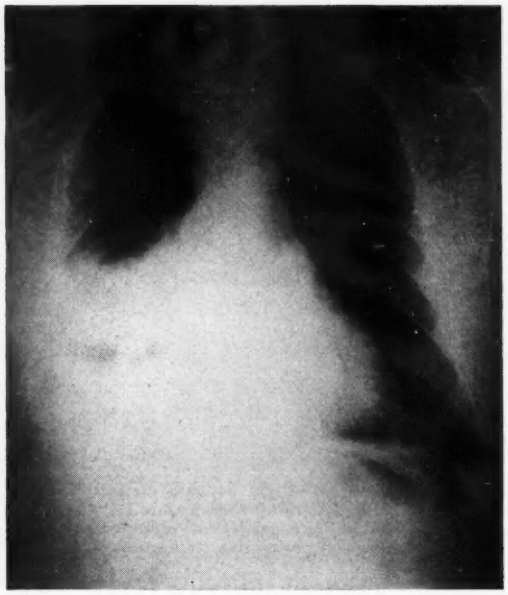

Figure 3 (Case 2).—Proved epidermoid carcinoma of right main stem bronchus. Left lung clear.

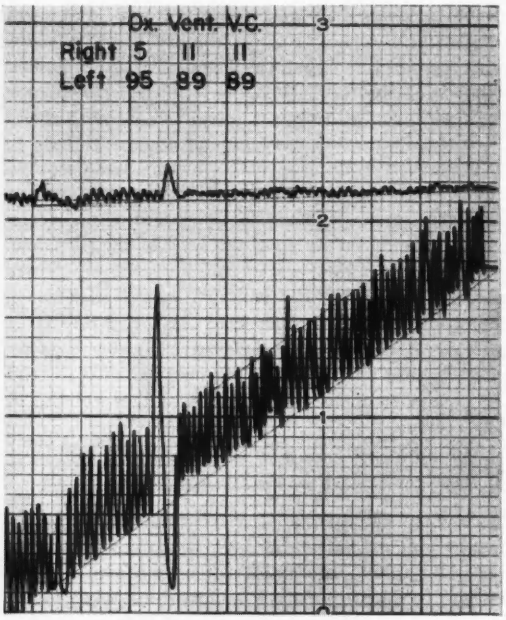

Figure 4 (Case 2).—Bronchospirometry shows almost complete dysfunction of the right lung (upper tracing) and normal function of the left. Prediction was satisfactory reserve on left to carry the whole load following right pneumonectomy. (Ox.=Oxygen uptake; Vent.=Ventilation; VC=Vital capacity—all expressed in per cent of total for both lungs.)

fuse rather than localized pulmonary disease and do not present surgical problems. Occasionally, a patient with old healed miliary tuberculosis and final localized disease may offer a problem with regard to oxygen transfer—in other words, may have an "alveolar-capillary block." Patients are occasionally referred to a thoracic surgeon for lung biopsy for definitive diagnosis or treatment on medicolegal problems. Severe "alveolar-capillary block" in these patients makes them a bad surgical risk for any intrathoracic procedure, including biopsy. This syndrome also offers a differential diagnostic problem in patients proposed for mitral valve operations who also have evidence of severe pulmonary infiltration. A few simple clinical findings which may point to the diagnosis of "alveolar-capillary block" may be mentioned here:

1. Evidence of diffuse miliary pulmonary infiltration on the x-ray film of the chest;
2. Normal maximal breathing and timed vital capacities;
3. Slightly to greatly reduced total vital capacity;
4. Respiratory alkalosis as evidenced by decreased carbon dioxide content and increased pH of the arterial blood; and, most important,
5. An increased dyspnea index or diminished breathing reserve due to increased ventilatory requirement rather than diminished breathing capacity.

Great discrepancies between the pulmonary function data and the patient's dyspnea are sometimes seen also in persons with neurocirculatory asthenia, in malingerers, and in persons with insurance claims.

Borderline functional reserve particularly deserves emphasis. Some thoracic surgeons still show a lack of interest—if not hostility—toward preoperative objective pulmonary functional evaluation. Some of them, discussing this subject, refer to an excellent operative record along with a low mortality rate due to pulmonary insufficiency as well as a low respiratory morbidity, as evidence in favor of clinical judgment only in the evaluation of surgical risks. Lacking, however, are data on the number and type of cases denied operation on the basis of clinical judgment only in estimating insufficient pulmonary reserve. On innumerable occasions Dr. Gaensler has carried out pulmonary function studies on patients of borderline risk who had been refused operation. It has been a matter of considerable interest that a number of them, after careful (and occasionally complex) testing, have been cleared for operation and have withstood the needed procedure without significant difficulty.

In considering inconsistencies between clinical impression and functional analysis of pulmonary reserve as well as borderline functional reserve when operation is imperative, the following cases are illustrative.

Case 2. The patient, a 59-year-old man with a proved epidermoid carcinoma of the right main

stem bronchus, had shortness of breath that had increased over an eight-month period and was out of proportion to other clinical observations. Right pneumonectomy was contemplated and it was imperative to know if the left lung could carry the respiratory burden alone, considering the degree of shortness of breath in the preliminary studies.

An x-ray film of the chest (Figure 3) showed the tumor mass in the right hilar region, supposedly some fluid (although none could be obtained) and a clear left lung.

Results of pulmonary ventilatory studies were:

	Predicted	Determined	Per Cent of Predicted
Maximal breathing capacity (liters per minute)	124	53	42
Vital capacity, cubic centimeters	3,995	2,100	52
One minute timed vital capacity, per cent of total	75	75	100
Air velocity index	1.0	0.80	....
Walking dyspnea index, per cent	15	45	....

The maximum breathing capacity was greatly reduced, but only slightly more than the vital capacity in per cent of predicted. Therefore, the air velocity index of 0.80 was nearly normal, indicating an absence of significant obstructive insufficiency. This was confirmed by the one-second timed vital capacity, which was normal. The walking dyspnea index showed that 45 per cent of the maximal breathing capacity (instead of a normal 20 per cent) was required during a leisurely walk at the rate of 180 feet per minute. Therefore, no obstructive defect was present.

The preliminary impression from the tests was of a moderately severe restrictive ventilatory insufficiency. Right pneumonectomy was considered possible provided the right lung did not contribute very much to total function.

Bronchospirometry for determination of the function of each lung separately showed that the right lung contributed only 5 per cent to the total oxygen uptake, 11 per cent to the ventilation and 11 per cent to the vital capacity (Figure 4). In other words, the patient already had, in physiologic effect, pneumonectomy of the right lung. It was thus determined that the left lung could carry the load alone and the patient was approved for right pneumonectomy.

CASE 3. The patient, a man 59 years of age, had had increasing shortness of breath over a period of five years. He had a proved carcinoma of the left main stem bronchus with wheezing cough and considerable mucoid sputum for three years. He appeared to be very short of breath but preliminary studies were not adequate for determining whether the right lung could carry the load if left pneumonectomy were performed.

An x-ray film of the chest (Figure 5) showed the tumor mass in the left hilum with lateral extension

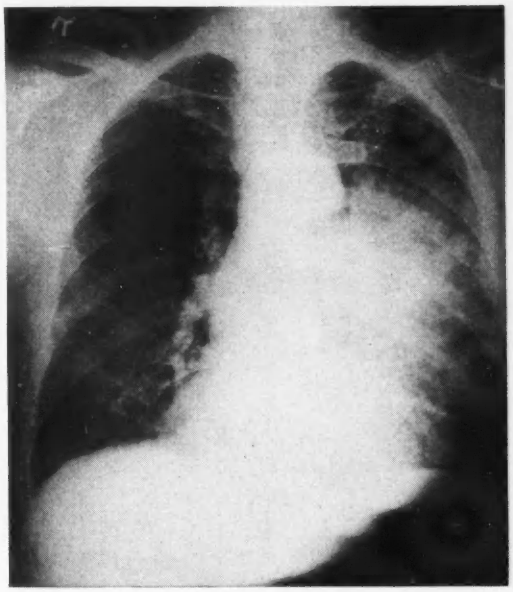

Figure 5 (Case 3).—Proved carcinoma of left main stem bronchus with lymphogenic spread through lung parenchyma. Right lung clear and not especially emphysematous in appearance.

of the process but not much evidence of atelectasis.

Results of pulmonary ventilatory studies were:

	Predicted	Determined	Per Cent of Predicted
Maximal breathing capacity (liters per minute)	119	36	32
Vital capacity, cubic centimeters	3,900	2,940	75
One minute timed vital capacity, per cent of total	75	35	47
Air velocity index	1.0	0.42	....
Walking dyspnea index, per cent	15	70	....

The maximal breathing capacity was reduced to one-third of normal and the vital capacity reduced to three-fourths of normal, thus giving a very low air velocity index of 0.42. This, together with severely reduced one-second timed vital capacity, indicated severe pulmonary insufficiency of the obstructive type. Functional incapacity in this case appeared to be due to advanced emphysema rather than to the carcinoma. Therefore, determination of individual lung performance was needed for final decision regarding the suitability of the patient for operation. Results of bronchospirometric studies (Figure 6) showed the right lung contributing a nearly normal share of function—43 per cent of oxygen uptake, 31 per cent of ventilation and 39 per cent of the vital capacity. It was clear that in the presence of this degree of obstructive emphysema the right lung could not carry the load alone after left pneumonectomy. Operation was not advised. Treatment with nitrogen mustard and x-ray therapy was

recommended and carried out with transient symptomatic relief.

CASE 4. The patient, a 26-year-old woman, had had therapeutic pneumothorax on the right from 1943 to 1948 with a good collapse, and left extrapleural pneumothorax from 1944 to 1947 for upper lobe cavitary disease. Attempted reexpansion of the right lung was not very successful and was followed by a tuberculous effusion. Two years after reexpansion of the left extrapleural pneumothorax, a new exudative lesion developed in the left upper lobe.

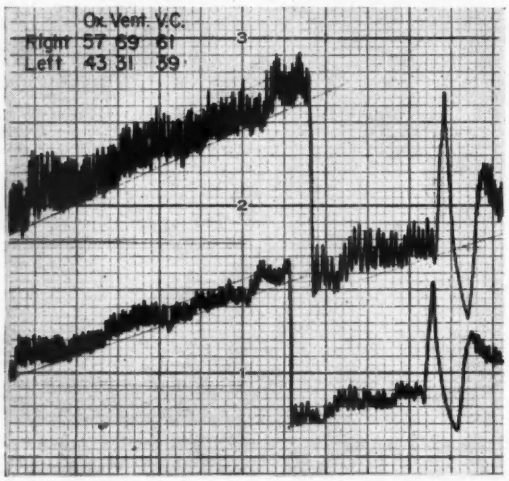

Figure 6 (Case 3).—Bronchospirometric studies show reduced functional oxygen uptake (Ox.) of the left lung (lower tracing and the side affected by the carcinoma) as well as decreased ventilation (Vent.) and vital capacity (VC) expressed in per cent of total for both lungs. But function on the right deemed not sufficiently better than the left to carry the whole load following left pneumonectomy.

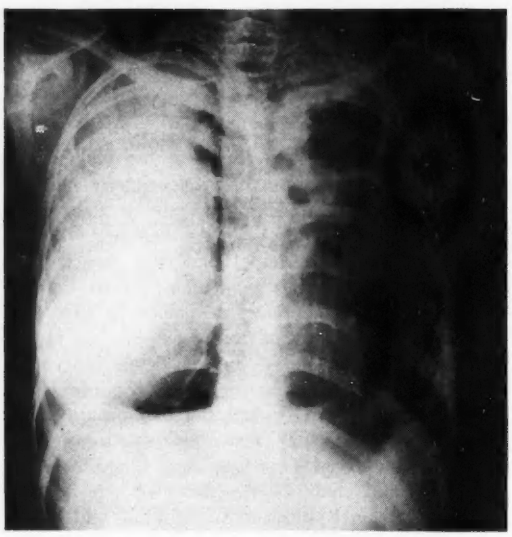

Figure 7 (Case 4).—Old dense pleuritis in right lung, obliterating lung markings, following attempted pneumothorax reexpansion in 1948. Left lung: Old fibrocalcific lesion and pleuritis at left apex and first anterior interspace. New exudative infiltration in area between second and third anterior ribs.

An x-ray film of the chest (Figure 7) showed extensive pleuritis involving most of the right lung with a localized effusion anteriorly placed. There was new infiltration with cavity in the left upper lung in the intraclavicular area.

It was felt that something might be done for the left lung if the right lung were found to be still in good condition beneath the pleuritis. Results of pulmonary ventilatory studies were:

	Predicted	Determined	Per Cent of Predicted
Maximal breathing capacity (liters per minute)	96	51	53
Vital capacity, cubic centimeters (normal timed capacities)	4,020	1,150	35
Air velocity index	1.0	1.51	....
Walking ventilation (liters per minute)	18	24	....
Walking index, per cent (slight dyspnea during walk)	19	45	....

The marginal performance was consistent with a restrictive rather than an obstructive defect. Bron-

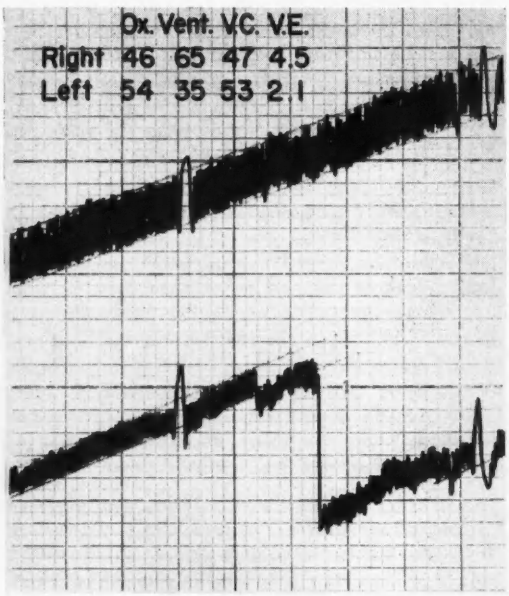

Figure 8 (Case 4).—Bronchospirometry showing better function on the right (upper tracing) beneath the pleuritis than was expected, but with decided restrictive defect as seen in the attempted deep breath of the vital capacity (VC). The left lung (lower tracing) shows better oxygen uptake (Ox.) and vital capacity but poorer ventilation—all expressed in per cent of total for both lungs. VE = Ventilatory equivalent (liters of air ventilated through the lung per 100 cc. of oxygen absorbed).

chospirometry was carried out (Figure 8) to determine the function of the right lung especially. It showed the right lung with surprisingly good function beneath the old pleuritis—oxygen uptake 46 per cent, ventilation 65 per cent and vital capacity 47 per cent. Yet the pulmonary reserve of the right lung was certainly insufficient to sustain life comfortably if function on the left were further diminished by excision or thoracoplasty.

Based on studies of Patton and co-workers,[8] the suggestion was made that a decortication be performed on the right and the patient then be reevaluated. This was done.

Figure 9 shows an x-ray film of the lungs after

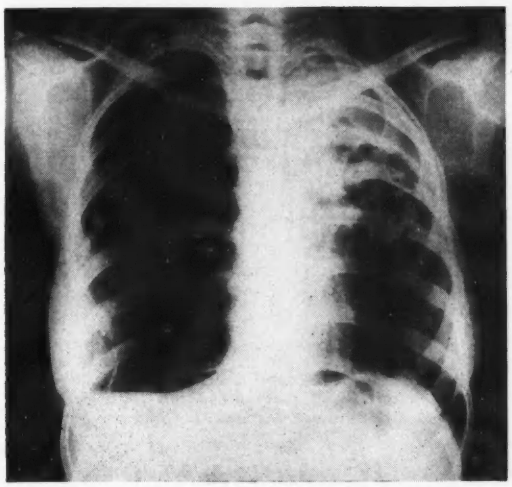

Figure 9 (Case 4).—Following decortication of thickened right pleura, with appearance of a remarkably healthy looking lung. Left lung essentially still unchanged.

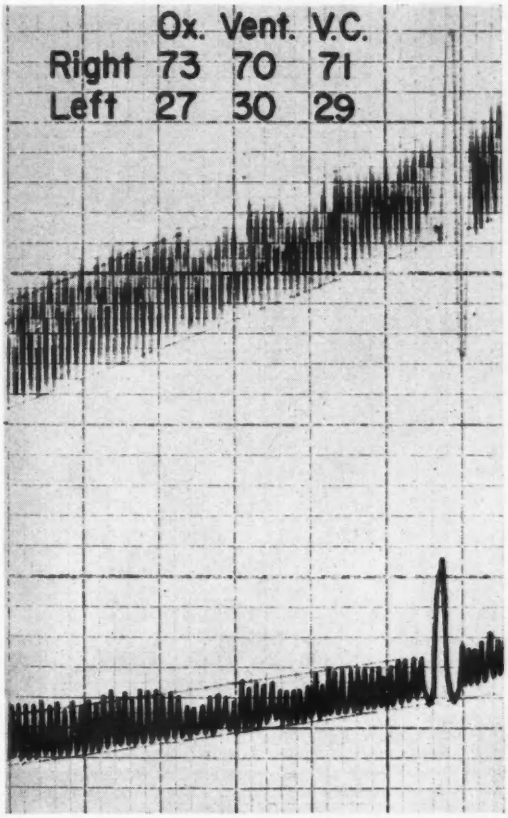

Figure 10 (Case 4).—This spirometric tracing shows excellent recovery of function in the right lung following decortication with loss of restrictive defect as seen in recovery of good ventilation (Vent.) and a good vital capacity (VC). (Ox. = Oxygen uptake—all expressed in per cent of total for both lungs.)

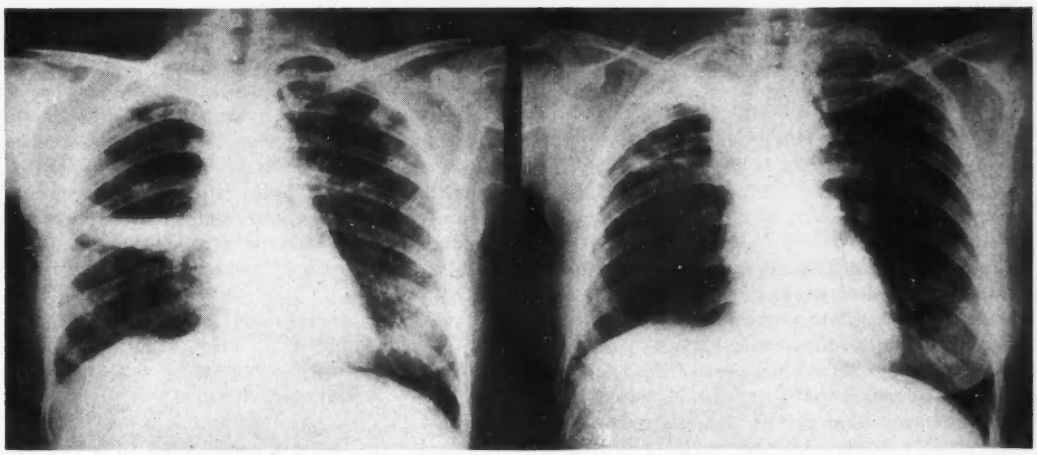

Figure 11 (Case 5).—X-rays before *(left)* and after four months of rest and chemotherapy *(right)*. This shows huge cavity with initial fluid level on the right side and scattered infiltration in left midzone. After four months of treatment there is reduction of cavity size with overexpansion of the right lower lung and decided clearing on the left.

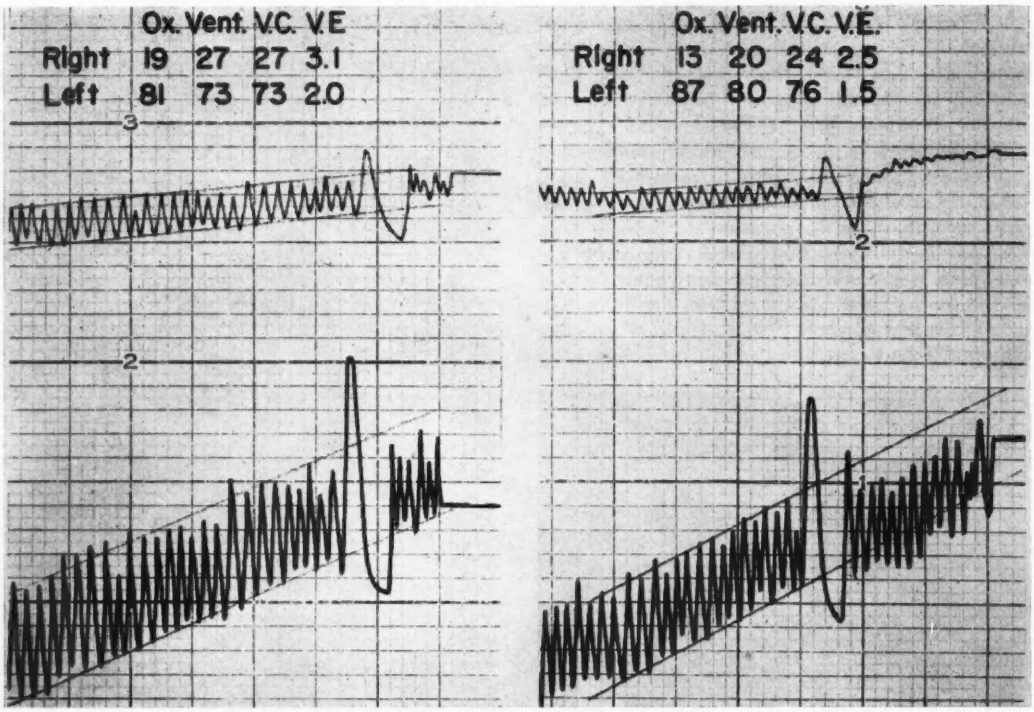

Figure 12 (Case 5).—Bronchospirometry before *(left)* and after four months of treatment *(right)*. Shows very little difference in the individual functional lung reserve, though a little worse on the right (upper tracing) and a little better on the left (lower tracing). It was anticipated that the left lung could carry the full load if a right pneumonectomy proved necessary at operation. Ox. = Oxygen uptake; Vent. = Ventilation; VC = Vital capacity—all expressed in per cent of total for both lungs. VE = Ventilatory equivalent (liters of air ventilated through the lung per 100 cc. of oxygen absorbed).

surgical decortication and wedge resection on the right. The right lung was remarkably clear. Ventilatory studies before and after operation showed improvement of function, as follows:

	Predicted	Before Decortication and Wedge Resection	After Operation
Maximal breathing capacity (liters per minute)	96	51	88
Vital capacity, cubic centimeters (timed capacity was normal)	3,280	1,150	1,800
Air velocity index	1.0	1.5	1.7
Walking ventilation (liters per minute)	16	23	16
Walking index, per cent (no dyspnea walking)	17	45	19

Bronchospirometric studies (Figure 10) seven months after decortication clearly depicted the pronounced functional improvement, the right side carrying 73 per cent of the oxygen uptake, 70 per cent of the ventilation and 71 per cent of the total vital capacity. It was felt that the right side could carry almost any load demanded of it. A left upper lobectomy was carried out without complication or respiratory embarrassment. Thereafter the patient was well and lived a normal life.

The Role of Function Studies in Determining the Extent of Operation

CASE 5. The patient, a tuberculous woman 36 years of age, the mother of a 4-month-old child with tuberculous meningitis, was herself completely free of clinical symptoms. In a comparison of films of the patient's chest before and three months after streptomycin-para-amino salicylic acid therapy along with bed rest, it was noted that a large cavity with a fluid level occupying more than half of the right lung before treatment was greatly reduced after treatment (Figure 11). Infiltration scattered over the midportion of the left lung also was greatly improved. The x-ray improvements from short-term therapy were not reflected in function studies.

	Predicted	Determined Jan. 21, 1952	Determined April 21, 1952
Maximal breathing capacity (liters per minute)	80	33	33
Walking dyspnea index, per cent.	17	40	40
Vital capacity, cubic centimeters	2,760	1,550	1,550
(Per cent in 1 second)	75	58	52
Air velocity index	1.0	0.73	0.73
Residual volume, cubic centimeters	700	.....	540
Residual volume: Total lung capacity ratio, per cent	20	.....	26
Pulmonary mixing index	1.5	.....	0.95

Studies of pulmonary function before and three months after the start of treatment showed marginal overall performance in both instances, with greatly reduced maximal breathing capacity and vital capacity, some slowing of the one-second timed vital capacity consistent with the slight increase of the ratio of residual volume to total lung capacity. This is primarily a restrictive defect without evidence of a minor obstructive element, seen in an air velocity index of 0.73.

Bronchoscopy showed a partially stenosed right upper lobe bronchus and a bent and therefore narrowed right lower lobe bronchus. The left bronchial tree was normal.

Bronchospirometric studies (Figure 12) before and after three months of chemotherapy showed the right lung contributing only 19 per cent of oxygen uptake, 27 per cent of ventilation and vital capacity with a slightly low ventilatory equivalent, that was due probably to the proportionately lower maximal breathing capacity. Here the question that arose was whether only the right upper lobe needed to be excised and the lower and middle lobes could be salvaged for their functional contribution later. At operation, disease was found scattered throughout all lobes on the right. Since the left lung had been shown to be carrying the respiratory functional load without difficulty, right pneumonectomy was found necessary and was carried out. Upon recovery the patient was well and lived a normal life of active work.

CASE 6. A 62-year-old man with far advanced emphysema was seriously incapacitated by dyspnea. An x-ray film showed carcinoma of the esophagus (Figure 13). Pulmonary function studies showed a maximal breathing capacity of 21 per cent of predicted, with a very large vital capacity of 91 per cent of predicted and, therefore, an extremely low air velocity index, indicating serious obstructive emphysema.

In spite of these findings and a recommendation against any transthoracic operation, the surgeon (whose faith in function studies resided chiefly in the vital capacity), noting that the vital capacity was 91 per cent of predicted, proceeded to resect the tumor through the left side of the chest under pentothal-curare-ether anesthesia. The patient died eight hours postoperatively of respiratory failure.

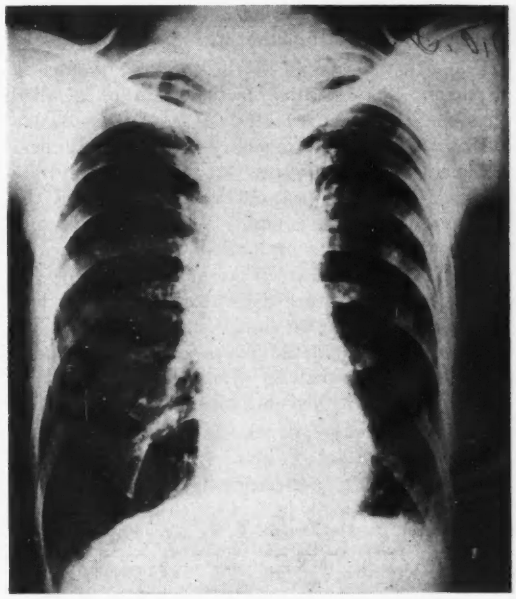

Figure 13 (Case 6).—Proved carcinoma of the esophagus. Upper mediastinal shadow greatly widened with apparent marked emphysema and low irregular diaphragm.

DISCUSSION

Preoperative pulmonary evaluation entails thorough investigation of the inconsistencies between the clinical impression of suitability for operation and the borderline functional reserve where operation is imperative. The area of pulmonary symptomatology unexplained by x-ray examinations and overall clinical estimations of function has been clarified by definitive pulmonary function studies.

Furthermore, the extent and type of surgical procedure to be planned for the best results, have been, in our experience, greatly influenced by the factual data of overall and individual lung function studies. The patient with good lung function can be evaluated with considerable success by the simpler techniques and by clinical judgment. Careful and searching function studies, however, are of the utmost importance for the patient with borderline pulmonary reserve.

In this latter group the decisions for or against operation are among the most difficult, and no stone in the documentation of pulmonary reserve should be left unturned.

Operation upon "poor risk" patients has been greatly enhanced by the advances in modern chemotherapy as well as in estimating pulmonary function. Middlebrook and co-workers[7] showed this in tuberculosis through newer concepts in drug therapy while advancing the "team concept" of the internist, the bacteriologist, the physiologist and the surgeon in not only preoperative evaluation of the pulmonary status but their cooperation throughout the course of the surgical procedures. Watson and Gaensler,[9] Woodruff[10] and others stressed that the type of pulmonary operation will be influenced by

the degree of disability as well as by the pattern and distribution of function within the lung.[5,6]

From the viewpoint of the internist and chest physician, the definitive factual data of detailed physiologic pulmonary studies are an invaluable aid in preoperative pulmonary evaluation. Clinical judgment alone will screen out the normal and the severely insufficient cases. There are, however, the many borderline and complicated cases that demand the most meticulous evaluation of pulmonary reserve. These studies are necessary in such circumstances not only to prevent operative fatalities and postoperative pulmonary crippling, but also in order that the benefits of operation may be made available to those patients who, on clinical grounds alone, might be denied this form of treatment.

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Pulmonary Heart Disease

A Panel Discussion

Participants: **MAURICE ELIASER, JR., *M.D.*, San Francisco, Moderator;**
HURLEY LEE MOTLEY, *M.D.*, and
MORTON L. PEARCE, *M.D.*, Los Angeles, and
ARTHUR SELZER, *M.D.*, San Francisco

DR. ELIASER: The discussion on pulmonary heart disease will be limited to the chronic form, or what has been termed chronic cor pulmonale. For expedience we shall discuss only those conditions in which cardiac or circulatory disturbances result from diseases of the lung or the pulmonary artery or its branches.

We shall exclude acute cor pulmonale and the various forms of right ventricular failure that are frequently associated with nonpulmonary conditions such as left ventricular failure and mitral stenosis. We shall also omit those lesions characterized by left to right shunts—namely, congenital patent ductus arteriosus, interatrial and interventricular septal defects and malformations in which the pulmonary veins empty into the right atrium or superior vena cava.

The panel will be primarily concerned with those chronic states where cor pulmonale results from either one or both of the following conditions:

1. Chronic diffuse obstructive emphysema.

2. Pulmonary vascular tree lesions—intraluminal or extraluminal and in combination.

The first thing that I would like to ask the panel, which, incidentally has representatives from both Northern and Southern California, is, "Has the incidence of pulmonary heart disease increased, and, if so, why?"

INCIDENCE

DR. PEARCE: The incidence of pulmonary heart disease is very definitely on the increase. Institutions that publish the incidence of various types of heart disease have shown a pronounced increase in this disease. Question arises as to whether this is because we now recognize it and didn't before, or is it really increasing. In my mind, there is no doubt at all that there is a decided increase in pulmonary heart disease and I suspect that as we keep people alive longer with chronic lung disease, as we do more thoracic operations, we are going to continue to see even more pulmonary heart disease.

DR. MOTLEY: That's my feeling also—that people are being kept alive longer today with better treatment both medically and surgically, and with the antibiotics life is prolonged until pulmonary heart disease may show up.

DR. ELIASER: These gentlemen, obviously, are from Southern California. Dr. Selzer, do you think it has anything to do with the air we breathe?

DR. SELZER: It may, but I would like to take the opposite standpoint in part. I think that the diagnostic facility and the accuracy with which we diagnose cor pulmonale now plays a part in the statistical increases; and my own observation has been that there may be certain overdiagnosis and we have on many occasions suspected cor pulmonale in patients with emphysema just to find out that they had the ordinary variety of coronary disease which happened to occur in patients with emphysema. It may be that the pendulum swung a little too far to the other side.

DR. MOTLEY: Could I interrupt just one second? I'd be interested to know what the feeling of the other members of the panel is about smoking.

DR. ELIASER: Do we have any volunteers?

DR. PEARCE: We're studying that aspect, but we have not been able as yet to show any quantitative difference from the standpoint of pulmonary function, either as to smoking or smog.

DR. ELIASER: We might go on to the classification of the various lung diseases that result in pulmonary heart disease. I think we agree that chronic diffuse destructive emphysema ranks No. 1 on our list. I would like to know if anyone on the panel would like to discuss the various causes of diffuse emphysema, including chronic bronchitis.

DR. PEARCE: As to the causes of diffuse obstructive emphysema: In almost all instances persons in whom the condition ultimately develops have a

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prolonged history of repeated pulmonary infections, usually with chronic bronchitis that flares up and subsides and may be associated ultimately with bronchiectasis. It is rather unusual to see a patient with late stages of a pure obstructive emphysema; there is always a degree of pulmonary fibrosis of restrictive aspect to the pulmonary disease as well as the obstructive aspect. Because of the important things we can do in prevention, it should be remembered that, almost always, obstructive emphysema is the late result of chronic pulmonary infection, with or without asthma.

DR. SELZER: I would agree with that. I think we probably should draw a very distinct dividing line between obstructive emphysema and the ordinary variety of senile emphysema (which some observers even refuse to call emphysema, using terms like senile kyphosis instead) in which the effect on the pulmonary function is relatively slight and the effect on the circulatory system is practically nil.

DR. MOTLEY: I'm one who feels that emphysema is not necessarily a part of the aging process. Our studies indicate that normally even in persons up to 70 years of age and beyond, the residual air is not above 35 per cent of total lung capacity. I know that there are some investigators who will disagree with this figure. Comroe in his book on the lung gives a figure as high as 50 per cent with no symptoms referable to the cardiopulmonary system. This is contrary to my experience. I feel the selection of cases for determining the upper limits of normal cannot be made alone from the x-ray studies or the subject's story, and that the clinical selection of what is considered normal may be misleading. If two criteria are used, (1) a normal maximal breathing capacity; and (2) a normal timed vital capacity, regardless of age, in my experience the residual air has not been found above 35 per cent of total lung capacity, so I don't feel that emphysema is part and parcel of the aging process normally. There are many persons with a residual air above 35 per cent of total lung capacity who are capable of doing their jobs and have no complaints. The reason for this is the big reserve in the lung normally, so that by the time subjective complaints of dyspnea are present the lung changes represent an advanced stage. I feel that residual air above 35 per cent of total lung capacity is abnormal, just the same as systolic blood pressure of 200 mm. of mercury is abnormal even though the individual may have no subjective complaints. Infection and bronchospasm are two very important etiologic factors in pulmonary emphysema. Also, there appears to be a hereditary factor—a difference in protoplasm, making some persons more prone to the stresses and strains that cause emphysema to develop. Smoking also appears to be an important factor in emphysema in some cases, although difficult to prove, for many heavy smokers never develop emphysema. It is of interest that practically all the patients I have observed with severe emphysema who have never been exposed to any kind of dust inhalation such as might produce emphysema (as silicate, diatomaceous earth or asbestos) do have a history of prolonged heavy cigarette smoking—two or three packs a day.

DR. ELIASER: Regarding the second major classification of pulmonary diseases, I should like to ask the panel what are the more common varieties of pulmonary vascular diseases that produce this condition, and what do we mean by alveolar capillary block?

ALVEOLAR CAPILLARY BLOCK

DR. SELZER: I think that alveolar capillary block simply means that there is difficulty in diffusion between the capillaries and the alveoli. I don't know whether we can consider this actually a circulatory disease. I think it is a disturbance in the gas exchange which does not necessarily lead to the condition that we are interested in here. I think perhaps one ought to state that the diagnosis of cor pulmonale or pulmonary heart disease is one of increased pressure in the pulmonary artery; in other words, what we are looking for is the effect of pulmonary hypertension on the heart, leading to its failure. We don't know what the relationship is between alveolar capillary block and pulmonary hypertension. I think perhaps we ought to separate the pulmonary function aspect of these diseases from the circulatory effect. They very often occur together but they also may be separate.

DR. MOTLEY: We have been interested in trying to get more precise information as to why the oxygen saturation of arterial blood is reduced in emphysema. When special tests were used, there appeared to be little evidence of a true diffusion difficulty at the alveolar-capillary membrane, such as typically occurs in beryllosis—which is a classic example of diffusion difficulty. The common finding in emphysema demonstrated every day is the presence of poorly ventilated alveoli, and with exercise most often a drop in saturation occurs, due principally to the shunting of blood through nonventilated areas or very poorly ventilated areas.

Two very simple tests can be used to demonstrate these findings. In the past few years a great deal has been written about the diffusion capacity of the lung. Reduced diffusion capacity of the lung is a general term and the condition may be due to several things and does not necessarily involve a true diffusion difficulty at the alveolar-capillary membrane with an increased arteriovenous gradient for oxygen

—for example, a reduced blood flow in pulmonary stenosis or in pulmonary hypertension with septal defect. The two simple tests entail high oxygen breathing and pressure breathing on air. In one the inspired oxygen tension is increased on a 32 per cent oxygen breathing mixture enough to overcome a diffusion difficulty, if that is the primary difficulty on air breathing. The decrease in saturation with moderate exercise, which occurs most often in emphysema, is not overcome—that is, saturation does not return to normal—even on the high oxygen mixture (32 per cent oxygen), thus demonstrating the absence of diffusion difficulty. The other test is the use of intermittent positive pressure breathing with compressed air only—no bronchodilators. In most cases of emphysema a significant rise in the saturation, sometimes up to normal, results from the pressure breathing on compressed air only; and the only way to explain this finding is on a basis of the presence of poorly ventilated alveoli, with the pressure breathing providing improved aeration.

Persons with emphysema have impaired movement of the diaphragm, loss in lung elasticity and increased breathing resistance, so that alveolar aeration is impaired and constitutes an important aspect in the blood gas exchange. If the saturation drops with exercise in a patient with emphysema, the low oxygen saturation represents a period of acute hypoxia. Acute hypoxia elevates pulmonary artery pressure and increases resistance. If the saturation drops 5 per cent or 10 per cent, the patient is advised not to walk up steps or uphill any more than he has to—or, if he lives on a second floor apartment, to get a first floor apartment. Every little acute episode represents an insult with a little increase in work load on the right side of the heart, and hastens the day right heart failure develops.

DR. PEARCE: My impressions are pretty much those which have been mentioned here—that is, that the primary difficulty leading to pulmonary hypertension in patients with cor pulmonale is basically one of distribution of gas to the right place and that alveolar capillary block is a relatively rare thing.

POLYCYTHEMIA

DR. ELIASER: The next thing we should discuss is the occurrence of polycythemia in pulmonary heart disease. Is it of any prognostic importance and does it help in differentiating between patients with considerable emphysema and those with little?

DR. PEARCE: This is an area in which I think you get many different impressions. Mine is that patients who get polycythemia fairly early in the course of pulmonary disease are the patients who tend to get cor pulmonale. Of course, by and large, they are the people with the most severe anoxia in the obstructive group, also the patients who have the most severe CO_2 retention.

DR. MOTLEY: My co-workers and I have been unable to make any correlation whatsoever between the hemoglobin values and the severity of pulmonary emphysema as measured by function measurements. If the hemoglobin is elevated we suspect a cardiac factor in emphysema. The oxygen capacity method, which I think is one of the more accurate measurements, is used to determine hemoglobin, and all of our experience has been at sea level pressure. There appear to be some differences between sea level and 5,000 feet altitudes like Denver and Salt Lake City, according to Dr. Hecht. Although there is no correlation between the severity of the emphysema and the hemoglobin level, if the patient starts going into the slightest degree of right heart failure, the hemoglobin level goes up. Hence, increased hemoglobin indicates the presence of some element of right heart failure.

DR. SELZER: It has been my impression that the relation between pulmonary heart disease, specifically pulmonary hypertension, and polycythemia is rather vague. There are enough cases of severe pulmonary hypertension other than emphysema in which there is no polycythemia; especially, many of the patients with so-called primary pulmonary hypertensions never get polycythemia and anoxemia. On the other hand, in dealing with emphysema, hypoxia is one of the factors in the production of cor pulmonale and is also a stimulus for the formation of excess hemoglobin, so that the relationship works in one direction but not in the other.

RESPIRATORY ACIDOSIS

DR. ELIASER: I should now like to bring up the rather interesting problem of respiratory acidosis. Is it of any significance in the differential diagnosis between the various forms of pulmonary disease, what are the conditions that produce it, and are there any factors that tend to accelerate its onset?

DR. PEARCE: Respiratory acidosis is the thing we all fear particularly in these cases, because it is at this point, when respiratory acidosis becomes severe, that the end is usually in sight unless the cause is something that is quickly correctable, such as a pulmonary infection. Respiratory acidosis is seen most commonly in the obstructive diseases. In those in which there is primarily an abnormality in the distribution of gases, anoxia occurs long before carbon dioxide retention does, because CO_2 as a gas is about 20 times more diffusable than oxygen.

DR. MOTLEY: Respiratory acidosis develops when alveolar ventilation is inadequate to blow off the carbon dioxide. The body is giving off almost as much

CO_2 all the time as oxygen is taken in, and, as Dr. Pearce has mentioned, the CO_2 in solution is about 25 to 30 times as diffusable as oxygen across the pulmonary membranes. Hence, for all practical purposes the CO_2 in the arterial blood is the same as in the alveoli—that is, the mean pCO_2* pressure. The determination of the arterial pCO_2 provides a measure of the adequacy of alveolar ventilation. If the arterial CO_2 content or pCO_2 is elevated, then alveolar ventilation is inadequate. However, one cannot determine from the CO_2 level whether the patient is in acidosis or not at the time. Many patients with severe emphysema always have high CO_2 levels. The pCO_2 may be 60 mm. of mercury or more (normal 40 mm. at sea level), yet the arterial blood pH be 7.45. In other words, they are compensated. The emphysema has developed over a period of years and they are compensated to the increased level. Trouble develops when such a person gets an infection with bronchospasm and plugging with mucus and secretions. The alveolar ventilation is reduced still more in the presence of little or no reserve and immediately the CO_2 goes up still more and the pH goes down below 7.38—that is, the arterial blood pH, which is the pH we must measure to have a guide of what is going on in the lung (venous blood is unsatisfactory).

The patient in acidosis requires prompt treatment to increase alveolar ventilation. The arterial blood pH is a real and indispensable guide in determining whether or not acidosis is present in these people with severe degree of pulmonary insufficiency. In my experience the calculated pCO_2 values or the calculated pH values in chronic pulmonary insufficiency of severe degree are not accurate even when one knows the arterial CO_2 content; and the CO_2 combining power may be completely misleading.

CARDIAC OUTPUT

DR. ELIASER: Now I have a more difficult question. Why is it that some persons with pulmonary heart disease have ostensibly high cardiac output and some have low output?

DR. SELZER: We have been interested in this subject and have studied the cardiac output in a series of between 20 and 30 patients with cor pulmonale of various degrees of severity. In our experience the high output is very rare. We have had, I think, only one or two patients in whom the cardiac output was definitely abnormally high. There are some in whom perhaps in relation to their symptoms, the output appears to be higher than average but is still within the normal zone. I think most of these people sooner or later as they develop more circulatory disturbance go into low output failure—that has been our experience.

DR. MOTLEY: I would agree with that with regard to the resting values, and certainly with exercise they are unable to increase the cardiac output normally corresponding to the exercise given. Some patients almost seem to have a fixed level to which the output can be increased, only a few liters above the resting level, regardless of how much exercise is given. With the more severe exercise on a treadmill or bicycle, they'll just fatigue quicker. One simple test which reflects the ability to increase the pulmonary blood flow is the exercise oxygen uptake. If the exercise oxygen uptake does not increase to a degree corresponding to the degree of exercise given, and if the minute ventilation is within the normal range, this finding indicates that the pulmonary blood flow is reduced, and indirectly that pulmonary vascular resistance is increased.

DR. PEARCE: We have been looking for patients with high output failure, so-called, due to pulmonary disease, and we certainly have been able to find very few. We've done dilution output studies on a large number of patients with chronic lung disease looking particularly for this group. I think the point Dr. Motley makes is a very good one—that even when you do find patients with moderately elevated output (and we've found them even as high as 10 liters per minute) with exercise they are not able to raise their output at all.

CLINICAL ASPECTS

DR. ELIASER: We might now comment on some of the clinical aspects of this condition and inquire whether there are any bedside clues to the presence of pulmonary heart disease in either the patients' symptoms or in the detection of any specific physical signs.

DR. PEARCE: Well, as far as determining cor pulmonale in a sense of hypertrophied right ventricle in itself is concerned, I think this is difficult to do by clinical signs alone. Certainly one can be suspicious about it when one finds the pulmonary disease which one can commonly detect by physical signs, particularly obstruction and restriction of ventilation. I think that as far as the physical signs of right hypertrophy itself go, looking for the accentuation of the second pulmonic sound, as has been mentioned earlier here today, is not particularly helpful. I have found that the appearance of a diastolic gallop along the sternal border has been a more useful sign than the accentuation of the second pulmonic sound which, in patients with barrel chests particularly, is something you may never hear at all, even with an extraordinarily high pulmonary artery pressure.

*Abbreviation for partial carbon dioxide.

DR. SELZER: I would agree with Dr. Pearce's statement. I think if the chest is not too barrel-shaped, we can also pay some attention to the right ventricular type of pulsation, which is quite helpful in diagnosing right ventricular hypertrophy.

DR. PEARCE: Sometimes when you can't detect this pulsation along the left sternal border because of a large chest, you can sometimes feel it by hooking your fingers under the xyphoid process and then feel a very active right ventricle.

DR. MOTLEY: I think I might add that one should be on the lookout for pulmonary heart disease in a patient where the breath sounds are distant. The evaluation with the stethoscope and the physical examination of the chest is better correlated with the degree of emphysema by pulmonary function measurements than by x-ray films. The use of the stethoscope is definitely indicated in chronic pulmonary disease, although some have advocated throwing it away. So often the patient comes in with right heart failure, and the cardiologist treats the right heart failure, but sometimes overlooks the underlying pulmonary disease.

SPECIALIZED DIAGNOSTIC PROCEDURES

DR. ELIASER: We can now move on to some of the more specialized diagnostic procedures; for example, what are the indications for pulmonary function studies and which ones are more frequently used?

DR. MOTLEY: I think any case that presents the clinician with a pulmonary problem in which there is possibility that function may be impaired, demands a little further investigation. Spirograms offer a rather simple test that can be done very quickly. The information obtained consists of total vital capacity, timed vital capacity, and the maximal breathing capacity, with a further determination of the maximal breathing capacity after administration of a bronchodilating drug (a test for bronchospasm). Also, a record of the shape of the spirogram tracing is very desirable, because in emphysema there is a very characteristic pattern with prolongation of exhalations (in some instances up to 12 to 15 and 20 seconds or more). One can often get some very useful information by asking the patient to take a deep breath and then to blow out as rapidly as possible. If the blow out is prolonged for 10 to 15 seconds, the extra time is very readily apparent; some patients even wheeze. Total vital capacity should never be used alone as a single measurement, as it may be misleading in some instances. The spirogram measurements may be indeterminate in some cases, or if the readings are either normal or extremely abnormal, that may be all that one needs in a particular case. If the spirogram measurements are moderately reduced, then we need to measure residual air to evaluate the severity of the emphysema. Residual air measurement is the only way that we have for accurately assessing quantitatively the degree of pulmonary emphysema.

Other tests, such as the use of a nitrogen meter with a single deep breath of oxygen or measurement of the nitrogen washout by individual breaths, require a complicated electrical set-up. The residual air is a simple measurement, but it is a laboratory and not an office procedure.

To complete the study, the blood exchange must be evaluated. Even though the patient may not have cyanosis, he may still have unsaturation and one must compare rest and exercise. Hemodynamically, rest and exercise represent two different situations in a given patient. The resting saturation may be almost normal, but exercise will bring out gross abnormalities. Arterial blood studies may be all that are needed in some cases. Exercise oxygen uptake has already been referred to as a very useful test and well correlated with complete function measurements where the pulmonary blood flow is reduced regardless of the cause, whether it be pulmonary emphysema or pulmonary hypertension with an atrial septal defect or with pulmonary stenosis. Anything that reduces the pulmonary blood flow will reduce oxygen uptake. Every case presents a specific problem, and in some just a few tests such as are provided by spirograms are in themselves adequate, or they may point the need for more complete study. I know of some physicians who have the Collins 13.5 liter respirometer in their office (probably the best apparatus for obtaining this information). I know of one chest physician who takes a spirogram on practically every patient who is getting an x-ray film of the chest.

DR. SELZER: I have nothing to add to the pulmonary function studies. I think, however, that it should be emphasized that in cor pulmonale there is no other way of actually knowing what one is dealing with than by cardiac catheterization. Pulmonary artery pressure at rest and exercise cannot be judged by any other indirect means.

DR. PEARCE: The only thing I have to add to what has been said is that in the very ill patient where the tests of respiratory function are very difficult to do, when we have acute situations in the hospital we find that frequent determination of the pH and the CO_2 content of the arterial blood gives the most help in determining which way they are going. I might say here parenthetically to beware of the report of CO_2 combining power on venous blood which has been suggested by some observers to be a good measure of CO_2 retention. This is a real booby trap, I think.

TREATMENT

DR. ELIASER: Now, as to treatment. I should like to bring up one question. There was a concept several years ago that digitalis may be bad for patients with pulmonary heart disease or that it may not do very much good. I'd like to get an expression of opinion from the panel: Should patients with pulmonary heart disease who are in congestive failure receive digitalis and, if so, which one of the glycosides?

DR. PEARCE: I think they should by all means receive the glycosides and I'm not particularly partial as to which they receive. Unless I'm in a hurry, I generally use digitalis leaf. Some of the bad results in the use of glycosides in these patients have been due to treating only the myocardium and not treating the pulmonary infection and obstruction in the patient with severe emphysema who is in failure.

DR. SELZER: Dr. Eliaser, I think that the concept that you mentioned originated in England; I think they may have changed their views since, and they all agree that digitalis is not contraindicated. However, I think it is very strongly disappointing in cases of cor pulmonale. When we use it, and I think we should, we very seldom see any spectacular effect.

DR. ELIASER: Another controversial therapeutic measure is phlebotomy. When should that procedure be used, and what should be used as a criterion for discontinuing it?

DR. SELZER: This is a subject of considerable controversy, for polycythemia increases the oxygen-carrying capacity and in a way is considered a useful compensatory measure. Most physicians feel, however, that it overshoots usefulness and may become harmful. One should try not to expect too much of phlebotomy in moderate polycythemia, but when the packed cell volume is 60 per cent or more, bleeding should be done to bring it down to about 55 per cent.

DR. ELIASER: I'm about to carry coals to Newcastle. Dr. Motley, when is intermittent positive pressure breathing indicated and what are its contraindications, if any?

DR. MOTLEY: I feel that intermittent positive pressure breathing (IPPB) has a very definite place in the treatment of chronic pulmonary disease. In severe emphysema IPPB is the most efficient method for the administration of bronchodilators and antibiotic, if the patient has an infection in which an antibiotic is indicated. The main function of the lung is to get oxygen into the blood and get rid of CO_2 adequately, and physiological studies indicate that IPPB improves this function in emphysema. Secondly, intermittent positive pressure breathing promotes bronchial drainage and helps raise secretions. This has been observed especially in coal miners as a group. Coal miners who have been away from the mines for as long as two years have started spitting black soon after IPPB was started. The third aspect with IPPB is breathing exercises. A lot has been written on breathing exercise, but in my experience it is hard to get patients to systematically take breathing exercises that are effective, and often in severe emphysema they cannot take effective breathing exercises. A patient with emphysema may be fluoroscopically observed to have very little movement of the diaphragm and a shallow type of breathing, but when fluoroscopy is repeated with IPPB increased movement of the diaphragm and deeper ventilation may be seen; and this is reflected in the arterial blood studies, for the oxygen tension goes up and the CO_2 goes down with administration of compressed air only (no oxygen with bronchodilators). The net result of IPPB is to keep the airways open by more effective treatment of bronchospasm and promoting bronchial drainage.

Follow-up studies, after three years, of patients with severe emphysema who have their own IPPB units for use at home and who have taken the treatments regularly and properly have shown that the residual air was not increased. I think that the only way patients with severe emphysema can hope to obtain the maximum benefits possible from the use of IPPB is to have a unit for use at home where, to start with, they may take three or four treatments a day of 15 to 20 minutes each. Eventually the number of treatments may be cut down to one or two a day in the less severe cases. However, the patients are going to require treatments for emphysema for the rest of their lives, as this condition tends to be slowly progressive; and unless one can prevent progression of the increased residual air (the best method to evaluate changes over long periods) the course is progressively downhill. Patients with emphysema often date the beginning of illness from an infection which calls it to their attention, although the emphysema has been present for many years, slowly progressive. Intermittent positive pressure breathing should be used in conjunction with all the other treatments indicated, such as use of diuretics, digitalis, low sodium diet, antibiotics and wetting agents. IPPB can be used in conjunction with tracheotomy, and in a few cases this has been life saving. IPPB can be used to supplement the Drinker respirator, especially with tracheotomy. The emphysema patient gets an infection, bronchospasm and the smaller bronchioles become plugged, alveolar ventilation is decreased, CO_2 increases, and respiratory acidosis develops; death then follows unless something is done about improving alveolar ventilation, and supplementary pressure breathing may be required continuously for several days.

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End Results in Parotid Tumors

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ALTHOUGH THERE HAVE BEEN many excellent papers published recently on the subject of parotid tumors, many important questions relative to the natural history and management of these lesions still remain either unanswered or neutralized by diametrically contradictory statements.

Unfortunately, the means usually resorted to for solution of problems of this type is a review of many cases documented by a large and varied group of clinicians, with operation done by numerous surgeons, often histologically reviewed by different pathologists and finally analyzed by one or several members of a writing team who interpret the findings of the others as best they can by making due allowances for omissions in the notations and by grouping together various facts of numerous observers who have used different and varied nomenclature. Anyone who has tried to make such an analysis of the charts of others realizes how much he has to read into and between the lines and how often he has to decide whether one historian uses "pigmented lesion" to mean black while others mean brown or red, and whether a "large" lesion is 1 cm. or 10 cm. in diameter and if a "nonpalpable node" was really palpable, and vice versa. The list of such variables could be extended. The errors possible in this kind of analysis can be compounded if the group analyzing the charts hands them over to a third echelon for final interpretation and analysis. It is, therefore, obvious that the more one can reduce the many variables involved in such an analysis, the more objective should be the end results. The validity of the conclusions will be inversely proportional to the number of variables involved in the study. In the present study such an attempt has been made by only including cases of parotid tumors managed by one surgeon who also carried out the follow-up observation and analyzed the data.

• **Management of parotid tumors can be based on a clinical classification of these lesions as being either "encapsulated" or infiltrating.**

The Warthin tumor (papillary cystadenolymphomatosum) is a benign encapsulated tumor, often occurring multicentrically or bilaterally especially in the lower pole area of the parotid. It is characterized clinically by its softness and fluctuation in size and a high incidence in elderly men.

The so-called "capsule" of well demarcated mixed and mucoepidermoid tumors is represented by a condensation of host fibrous stroma, in the interstices of which tumor cells may be present.

The "encapsulated" tumors should be excised with a "shell" of uninvolved parotid tissue. To do this safely, the facial nerve should first be isolated.

Total parotidectomy is necessary only if the size of the tumor, the multiplicity of recurrences, or the infiltrating nature of the tumor are such that complete eradication of the primary site must be done.

Radical neck dissection is never performed electively except in the small group of nonencapsulated infiltrating primary lesions.

In a series of cases of previously untreated parotid tumors treated by the method outlined, the local parotid recurrence rate was less than 1 per cent.

MATERIAL

The material was 218 cases of parotid tumor in which the patients were observed for periods of one to nine years. Many questions can be answered on the basis of a follow-up of this length, while the answers to others will require even longer periods.

Presented before the Section on General Surgery at the 85th Annual Meeting of the California Medical Association, Los Angeles, April 29 to May 2, 1956.

From the Department of Surgery, Cedars of Lebanon Hospital, Los Angeles.

METHOD

In all cases surgical operation was done (see Figures 1 to 6). External radiation was used postoperatively in certain selected cases. The type of operation was standardized and therefore performed in the same manner in all cases. Only the extent of the operation was varied, but on one basis only—the extent of the disease.

Most parotid tumors are well defined and limited by a so-called capsule. This "capsule" (directly related to the slow growth of the tumor) is only a condensation of the host fibrous stroma in the interstices of which are islands or clumps of tumor cells. The surgical objective, then, is complete removal of the tumor and the "capsule." To do this an intact shell of uninvolved parotid tissue around the palpable mass must be taken. It is only rarely necessary to do total parotidectomy to accomplish this purpose. Even then, total parotidectomy is never performed "en masse" unless the facial nerve is totally sacrificed. Technically, if the nerve is spared, a total parotidectomy is performed piecemeal so that tiny

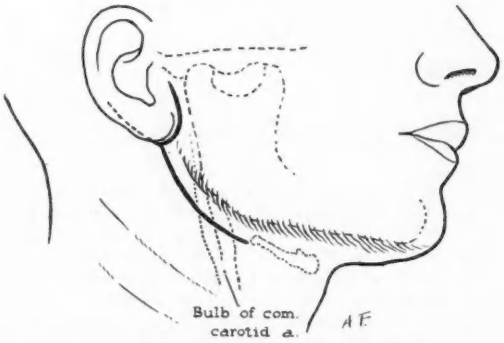

Figure 1.—Illustrating the "Y" incision with the preauricular arm placed in a natural wrinkle very close to the tragus and the cervical arm paralleling an adjacent neck crease as it is extended to the tip of the hyoid.

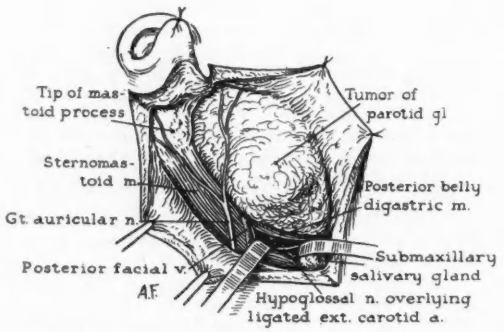

Figure 2.—The anatomical landmarks displayed after elevation of the skin flaps. The external carotid artery may be ligated at this time just caudad to the posterior belly of the digastric muscle.

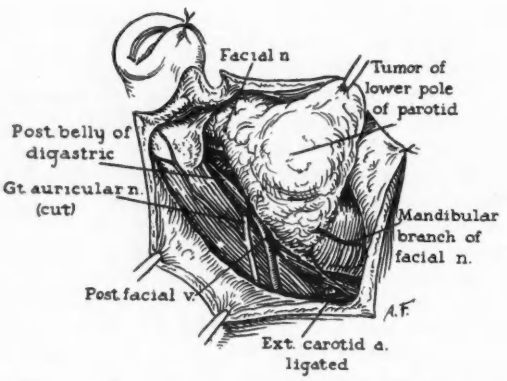

Figure 3.—By tracing the posterior belly of the digastric muscle to its origin on the medial surface of the mastoid process, the main stem of the facial nerve is identified as it lies 1 to 2 cm. deeply medial to this point. When the volar surface of the tip of the index finger is placed on the medial surface of the mastoid, the nail will be in contact with the main stem of the facial nerve.

remnants of parotid tissue are left "in situ" in all instances.

Total parotidectomy is often recommended because of the multicentric nature of these "encapsulated" tumors. The rarity[3] of such an occurrence in previously untreated cases makes this recommendation entirely invalid. Presumably the high percentage of multicentricity refers to cases in which operation has been done and inadequate excision or enucleation has left remnants of capsule with attached tumor cells in the perimeter of the tumor bed. From these multiple points growth may take place into the previously made surgical field, giving rise to a false genetic manifestation of multicentricity.

In the present series no attempt was made to deliberately do a total parotidectomy as a finite procedure. If the tumor was such that total or almost total parotidectomy was necessary to extirpate it, this procedure was performed; and in such instances it was often necessary to include extraparotid tissue such as skin, fat, fascia or muscle in the excision.

In all cases the facial nerve was isolated, and always at one point only—where the main stem emerged from the stylomastoid foramen. None of the other avenues of approach for isolation of the facial nerve branches was utilized in this series of cases. In previously untreated cases, regardless of the histologic diagnosis or size of the tumor, the facial nerve was never sacrificed—with the one exception of cases of infiltrating nonencapsulated malignant tumor wherein the facial nerve was embedded within the substance of the spreading tumor. Even in such cases, unless the surgeon is prepared to remove the adjacent condemned areas such as the masseter muscle and possibly the auricle, the external auditory canal and part of the mandible and mastoid,

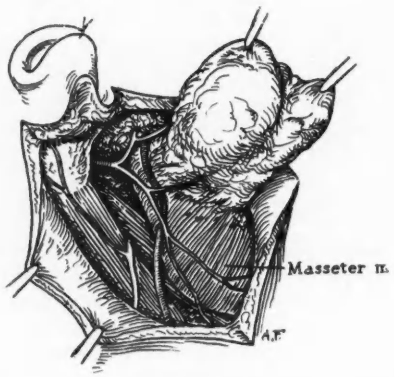

Figure 4.—While dissecting out the branches of the facial nerve, the superficial lobe of the parotid is elevated with its contained tumor. Note that the posterior facial vein is usually deep to the facial nerve.

there is nothing to be gained by simply sacrificing the facial nerve and leaving all or some of these involved contiguous structures "in situ." Simply removing the facial nerve with the parotid under such circumstances adds nothing to the surgical extirpation of local disease of this type, except that it makes the operation much easier.

Since the majority of such infiltrating tumors are much more radiosensitive than the average "encapsulated" parotid tumor and since a very high proportion of them (50 to 75 per cent) metastasize at least to the regional lymph nodes, the preferable course (unless one is prepared to perform wide radical excision of the primary site as previously mentioned) would be to perform a radical neck dissection in continuity with removal of all of the parotid gland, saving the facial nerve. Thus postoperatively the surgeon presents the radiologist with a more limited field for radiation, namely the primary site. The presence of the facial nerve in this field will in no way minimize whatever success the radiologist may have. It is believed that such a combination of modalities offers a greater opportunity of success in cases of this type than the use of either alone. This combined surgical and radiologic treatment was carried out in four cases in the present series.

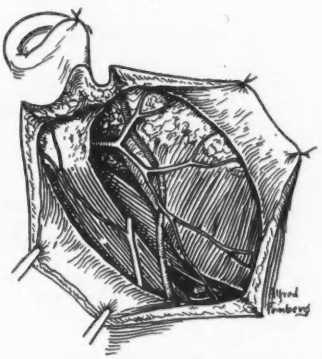

Figure 5.—If the tumor is in the deep lobe, the superficial lobe must first be removed as shown in Figure 4 and then the diseased deep lobe may be removed from beneath the facial nerve by elevating or spreading the branches.

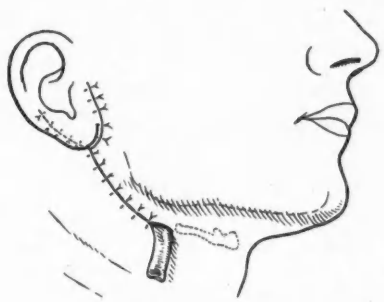

Figure 6.—Closure, showing site of drain.

The "Y" skin incision with the "hub" of the incision immediately below the lobe of the ear was used in all cases in this series.

The external carotid artery was ligated in continuity whenever it was felt that as bloodless a field as possible was necessary to avoid injury while locating the main stem of the facial nerve. This was particularly helpful in cases of large or incarcerated tumors of the pterygoid extension of the superficial lobe or in tumors of the deep lobe and in recurrent cases. The procedure can be performed through the same incision by extending the submandibular arm several centimeters toward the hyoid bone. The theoretical disadvantage of such ligation—that is, that it would interfere with the clean performance of neck dissection later, if that were indicated—can be dismissed as being of little importance when one considers that the incidence of subsequent cervical node involvement in such cases is less than 1 per cent.

When the preauricular area of the parotid gland is approached during the dissection, careful search is made for large tributaries of Stensen's duct. When these tributaries are isolated and transected, the cut distal ends are tied with fine silk to reduce the possibility of prolonged fistula formation.

Elective radical neck dissection was never performed, as fewer than 1 per cent of these tumors ever spread to regional lymph nodes after the primary lesion was controlled. In cases in which the homolateral cervical lymph nodes were involved and in all cases of infiltrating primary lesions, therapeutic radical neck dissection was performed either in continuity if the involvement was known at the time of operation or as a second stage when involvement became manifest later.

RESULTS

In the 218 cases of parotid tumor 121 were mixed tumors, 29 mucoepidermoid tumors and 18 Warthin's tumors. The present analysis deals with those cases. The tumors of other categories were too few in number for valid analysis (Table 1).

The age range of patients with mixed and mucoepidermoid tumors was from 16 to 82 years; of those with Warthin's tumor, 48 to 83 years (Table 2). The incidence of Warthin's tumor was considerably higher in men than in women; for mixed and mucoepidermoid tumors the converse was true (Table 3). Warthin's tumors were located predominantly in the lower pole of the superficial lobe of the parotid and only 11 per cent in the deep lobe; the mixed and mucoepidermoid tumors were in the

lower pole in a considerably smaller proportion of cases (Table 4). These data raise strong suspicion of a Warthin's tumor if the patient is an elderly man and the lesion is "encapsulated," is located at the lower pole of the parotid, and especially if, in addition, it is somewhat soft and varies in size from time to time.

For removal of the tumors, subtotal parotidectomy was done in 128 of the 168 cases and total parotidectomy in 40 cases (Table 5). In only seven instances was radical neck dissection performed in continuity because of the presence of clinically involved nodes or an infiltrating primary tumor. In one instance a staged procedure was done. In that case there was no clinical evidence of cervical involvement, but subsequently there was found to be metastatic extension to a cervical node in proximity to the lower pole of the superficial lobe of the parotid gland, where an "encapsulated" mucoepidermoid tumor was located.

In no case in the series was there accidental injury of the main stem or a major branch of the facial nerve. In six cases deliberate transection of the main stem was done, in four of them because of presurgical paralysis and in two because of intimate tangling of the nerve in the crevices of huge recurrent tumors (Table 6). The latter were really multicentric foci of recurrent tumors which became fused in conglomerate masses, trapping the nerve branches adhesively within the substance of the entire blob.

TABLE 1.—*Description of Parotid Tumors (218 Cases)*

Kind of Tumor		No. of Cases
MALIGNANT TUMORS (186 CASES)		
A. Primary (160 cases):		
1. Mixed tumors		121
2. Mucoepidermoid tumors		29
3. Acinic cell tumors		2
4. Lymphomas		8*
Lymphosarcoma	5	
Giant follicular lymphoma	1	
Hodgkin's disease	1	
Lymphatic leukemia	1	
B. Secondary (26 cases):		
1. Metastatic (15 cases):		
		Primary Site
(a) Melanoma	11	Skin
(b) Squamous cell carcinoma	2	Ear, tonsil
(c) Lymphosarcoma	1	Tonsil
(d) Fibrosarcoma	1	Orbit
2. Direct extension (11 cases):		
(a) Squamous cell carcinoma		Ear, cheek, external auditory canal
(b) Basal cell carcinoma		Ear
(c) Adenocystic carcinoma		Cheek, skin appendage
(d) Ceruminous adenocarcinoma		Ear canal
(e) Fibrosarcoma		Mandible
(f) Rhabdomyosarcoma		Temporal muscle
BENIGN TUMORS (32 CASES)		
1. Warthin's tumors (papillary cystadenolymphomatosum)		18
2. Benign lymphoepithelioma (Godwin)		3
3. Hemangioma		2
4. Lipoma		4
5. Epithelial cyst		5

*The lymphomas in this primary group were invariably within peri- or intraparotid lymph nodes without clinical evidence of disease elsewhere.

TABLE 2.—*Data on Age of Patients in Relation to Kind of Tumor*

	No. of Cases	Age of Patient (Years) Range	Average
Mixed tumor	121	16 to 76	46
Mucoepidermoid tumor	29	18 to 82	50
Warthin's tumor	18	48 to 83	65

TABLE 3.—*Relation of Kind of Tumor to Sex of Patient*

	No. of Cases	Male (Per Cent)	Female (Per Cent)
Mixed tumor	121	30	70
Mucoepidermoid tumor	29	38	62
Warthin's tumor	18	72	28

TABLE 4.—*Location of Various Kinds of Parotid Tumors*

	(Per Cent of Total Number of Each Kind)			
	Superficial Lobe			Deep Lobe
	Preauricular Area	Lower Pole	Pterygoid Extension	Includes Intra-oral and Duct Lesions
Mixed tumor	14	23	33	30
Mucoepidermoid tumor	21	17	24	38
Warthin's tumor	6	72	11	11

TABLE 5.—*Data on Kinds of Operations Used in Dealing with Various Kinds of Parotid Tumors*

	No. of Cases	Kind of Operation: Parotidectomy Subtotal	Parotidectomy Total	Neck Dissection In Continuity	Neck Dissection Staged
Mixed tumor	121	98	23	2	1
Mucoepidermoid tumor	29	13	16	5	0
Warthin's tumor	18	17	1	0	0
		128	40	7	1

TABLE 6.—*Data on Postsurgical Paralysis in Cases in Which Facial Nerve Was Transected*

	No. of Cases	Presurgical Paralysis	Postsurgical Result
Total transection	6	4	Two permanent
Buccal transection	9	0	Total recovery in 17 to 450 days
Mandibular transection	7	1	Five recovered in 120 to 600 days; 1 permanent

This never occurs with previously untreated "encapsulated" tumors, even large ones, because the nerve branches in such instances are either stretched over the surface of the mass or, at the most, embedded in a crevice of the nodular tumor and separated from it by an easily removed specific fascial layer. In addition nine smaller buccal branches and seven smaller mandibular branches were deliberately transected in recurrent cases because of the increased possibility of further recurrences, the intimate adherence to these nerves and the apparent unimportance of these branches. The estimate that they were unimportant was borne out by the fact that in all but one instance function returned completely in two weeks to two years.

Salivary fistula occurred in only 6.5 per cent of patients who had subtotal parotidectomy and all cleared spontaneously in 15 to 87 days. Searching for and tying off major duct branches with nonabsorbable fine silk may have been an important factor (Table 7).

TABLE 7.—*Data on Occurrence of Salivary Fistulae in 168 Cases of Parotidectomy*

Occurred in 11 cases (6.5 per cent).
Extent of operation—8 subtotal parotidectomies; 3 total.
Previous operation—3 cases.
Location of tumor—Preauricular area 4; lower pole 4; pterygoid extension 2; deep lobe 1.
Duration of fistula—15 to 87 days; average—32 days.

TABLE 8.—*Data on Development of Auriculotemporal Syndrome in 237 Cases of Parotidectomy*

Incidence:
24 per cent of all cases.
20 per cent of subtotal parotidectomies.
34 per cent of total parotidectomies.

Onset:
Two to 48 months after operation.
(Average—11 months).

TABLE 9.—*Data on Metastasis from Parotid Tumors of Various Kinds*

	No. of Cases	No. with Metastasis	Metastasis to Cervical Nodes	Metastasis to Distant Lung, Bones
Mixed tumor	121	3	1	3
Mucoepidermoid tumor	29	10	10	5
Warthin's tumor	18	0	0	0

TABLE 10.—*Data on Death from Disease in 168 Cases of Parotid Tumor in Which Operation Was Done*

Kind of tumor:
(a) Mixed tumor, 2 cases (1.5 per cent).
(b) Mucoepidermoid tumor, 7 cases (24 per cent).

Areas involved:
(a) Residual disease in parotid, 6 cases.
(b) Regional nodes involved, 8 cases.
(c) Distant metastasis, 6 cases.

The auriculotemporal syndrome was, surprisingly, found in 24 per cent of the entire series* (Table 8).

After many consultations with the group of pathologists involved, it was decided that the criteria for diagnosis of benign mixed tumors and low-grade mucoepidermoid tumors were either so nonspecific or borderline that from a clinical standpoint still other important variables would be eliminated by accepting all of these lesions as malignant. The impression was gained that genetically all the mixed and mucoepidermoid tumors had a common genesis, differing only in their growth potential, with the mucoepidermoid tumors representing the more malignant types. The Warthin tumor was considered to be a benign lesion, often multicentric and bilateral. Further, from a clinical standpoint, the management of these tumors was dependent on only two factors. First, whether the primary lesion was "encapsulated" or infiltrating, and, second, whether or not metastasis was present. In this series of cases nothing occurred during the one to nine-year period of observation to warrant a change in the utilization of this simplified classification as a basis for management. Using this clinical classification, it was found (Table 9) that a 0.8 per cent of the mixed and 32 per cent of the mucoepidermoid tumors metastasized to the cervical lymph nodes, and in all cases this occurred preoperatively. Distant metastasis, primarily to the lungs and bones, occurred in 2.5 per cent of the cases of mixed tumors and in 16 per cent of the cases of mucoepidermoid tumors—postoperatively in all cases. As was expected metastasis did not occur in cases of Warthin's tumor.

That patients die from parotid tumors is well known. In the present series there was a 1.6 per cent mortality in the mixed tumor group and 24 per cent in the mucoepidermoid tumors (Table 10). Death was due to distant metastasis in six of the nine cases and to the local effects of the disease in the other three cases.

Perhaps the most important criterion upon which the effectiveness of this method of management rests is that of recurrence in the primary site. McFarland[5] and others[1,2,4,9,10] showed that with simple enucleation, curettage, radiation or any combination of these therapeutic measures the local (parotid area) recurrence rate is from 15 to 65 per cent. The higher figure is perhaps the more dependable,

*The factors involved in this interesting sequela will be discussed in a separate paper.

TABLE 11.—*Local Recurrence*

Mixed tumor:		
Primary cases	(89)	1%
Cases previously operated on	(32)	18%
Mucoepidermoid tumor:		
Primary cases	(14)	None
Cases previously operated on	(15)	13%

since it is based on a study of a large group of cases over a long period of time.[5] In the present series (Table 11) there was only one local recurrence in a series of 103 cases, not previously treated, of mixed and mucoepidermoid tumors observed for a period of one to nine years after operation. On the other hand, with the same and even more extensive management applied to previously treated patients who had recurrence, the subsequent recurrence rate was 17 per cent.

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Percutaneous Trans-splenic Portal Venography

Applications and Hazards

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• **Trans-splenic percutaneous portavenography is a useful and relatively simple roentgen examination. Although infrequent, splenic hemorrhage and delayed splenic rupture sometimes do occur after splenic puncture. Hence the procedure should be used only with provision for immediate operation in case of hemorrhage.**

The method is invaluable in the demonstration of intrahepatic and extrahepatic portal obstruction, gastric and esophageal varices. With it, the size of the portasplenic veins and the degree of portal hypertension can be estimated.

EFFORTS TO MAKE the liver and spleen opaque to roentgen rays by means of contrast media have had a long and relatively unsuccessful history. The size and shape of the liver and spleen can be demonstrated by direct radiographic studies or by pneumoperitoneum but the internal structure of these two organs, their vascular supply and the changes which result from pathological processes cannot be clearly estimated in this way.

The introduction of cholecystography gave hope that the contrast substance used for demonstration of the gallbladder would also permit visualization of the internal structure of the liver, but the amount of contrast medium was too small in proportion to the large size of the liver and the hope was not realized. Various other methods for the study of the biliary duct system itself have been introduced and it is now possible to study adequately this portion of the liver by means of roentgen examination.

The introduction into the blood stream of a stable colloidal substance, Thorotrast,® which has a high opacity to roentgen rays and is absorbed by the reticuloendothelial cells of the liver and spleen, resulted in a brilliant demonstration of the size, shape, position and internal structure of these two organs. By this means, tumors of the liver, cirrhosis and various other diseases could be effectively portrayed. Unfortunately, this substance is slightly radioactive, but even more importantly, remains almost permanently within the liver. There is some evidence, in fact, that it may be slightly carcinogenic. Therefore, it has fallen into disuse for the roentgen study of this organ. Iodine has been put into various other molecules to make them radiopaque, but when injected as colloids all have shown toxic effects and they have not been widely used.

In 1950, Moore and Bridenbaugh[15] reported observations on a method of roentgenographically demonstrating the portal circulation by injection of 70 per cent Diodrast® into the right gastroepiploic vein during an abdominal operation. The right side of the portal circulation and the distribution of the branches of the portal vein within the liver were very effectively demonstrated. Furthermore, films made at suitable intervals after the introduction of a contrast substance directly into the portal circulation indicated that an opacification of the parenchyma of the liver could be produced by this method and some studies of the internal structure of the liver were made. Carcinomatous metastasis was thus successfully exhibited in the roentgenogram. This method is sharply limited since it can be used only when the abdominal wall is open.

Bierman and associates[3,21] demonstrated that it was possible to accomplish portal venipuncture by a percutaneous transhepatic approach. Likewise, in this way the portal circulation in the liver could be visualized in a roentgenogram. The method, however, has not attained wide clinical acceptance, perhaps because of reluctance to puncture the liver blindly.

Rigler, Olfelt, and Krumbach[17] were able to produce opacification of the liver through the medium of abdominal aortography. The liver was filled with contrast medium first through the hepatic and splenic arteries. Contrast also passed into the mesenteric vessels and thus was returned to the liver in the portal circulation. Films made at suitable intervals after injection exhibited an opacified liver in which various disease processes, especially metastasis, could be demonstrated. The method requires serial roentgenography and involves the hazard which attends abdominal aortography.

In 1951, Abeatici and Campi[1] extended the usefulness of the procedure of contrast visualization of the portal circulation by the development of a method of percutaneous splenic puncture, introducing the contrast material directly through the splenic

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pulp into the splenic vein and thus into the portal circulation. The excellent anatomic demonstrations which they achieved stimulated interest in the procedure and since that time many articles on this subject have appeared in the literature.[2,4,12,14,16,19,20] The largest series have come from European investigators who have felt that much information can be gained from this examination at a relatively low risk to the patient. A smaller series has appeared in American literature describing portal vein opacification by percutaneous transsplenic and transhepatic approaches and by direct injection of the splenic vein at operation. It is our purpose to add to our early experience with direct injection of the portal vein at operation, a later experience with percutaneous trans-splenic portal venography as a method of evaluation of portal hypertension and to mention some possible avenues of future application.

The method of percutaneous splenic puncture we used is similar to the methods used by earlier workers. However, we have felt that serious hemorrhage was a definite possibility following puncture of the spleen despite observations by others that this is a rare complication. To minimize this danger and to evaluate the degree of hemorrhage resulting, in all of cases puncture was done immediately preceding operation to carry out portacaval or lienorenal shunt. In most of the cases the patient was under general anesthesia at the time of puncture. In three cases local anesthesia was used. Having done puncture with patients both prone and supine, we believe successful entry into the spleen is facilitated when the patient is supine. A three-inch 20 gauge spinal needle is inserted through the left 9th or 10th intercostal space at the midaxillary line, the needle being directed slightly dorsad and cephalad. With endotracheal anesthesia, it is possible to have respiration held in the phase of expiration as the needle is advanced. Since the needle may cross the pleural space in some instances, this will reduce the possibility of pulmonary trauma. As the spleen is met, definite resistance can be felt. With patients not anesthetized, some pain may occur as the splenic capsule is penetrated. The needle is then advanced 2 to 3 cm., depending on the thickness of the spleen. Aspiration of a small quantity of blood indicates a successful puncture. This is followed by the injection of 20 cc. of 70 per cent Urokon® as rapidly as possible, using a 20 cc. luer-lock syringe. In patients not anesthetized, considerable pain follows injection, but it usually subsides in about 15 minutes. Little pain was experienced by one patient in whom a faulty puncture resulted in the injection of 20 cc. of the contrast medium into the peritoneal cavity. In about half of the cases in which we have used the method, entrance of the mass of Urokon into the

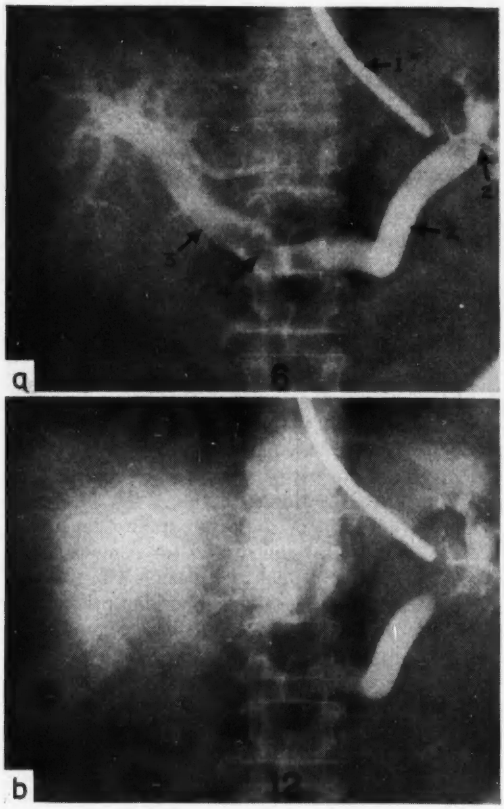

Figure 1.—Splenoportagram in a patient suspected of portal hypertension but now considered normal. *Above:* Film taken immediately after injection. (1) Gastric suction tube; (2) splenic vein; (3) portal vein; (4) decreased density resulting from dilution by noncontrast blood from mesenteric vein. The intrahepatic branches of the portal vein are well seen within the liver shadow. *Below:* Twelve seconds after injection. Some residual contrast still remains in the spleen and in the splenic vein. The opacification of the liver resulting from the passage of contrast blood through the sinusoids is well shown.

vascular system caused transient depression in blood pressure. None was serious and no other splenic complications occurred. Films of the upper abdomen, including the liver and a portion of the spleen, have been made at the rate of one per second, using an automatic rapid filming device. We have also done this by use of ordinary cassettes, changed manually, to obtain serial films at 4-second intervals over a period of about 30 seconds.

Successful splenic injection (Figure 1) was accomplished in all but two cases. The failures were early in our experience before the present technique was fully evolved. The majority of patients had enlargement of the spleen. When splenic enlargement is present, as shown by conventional abdominal films or by palpation, successful puncture should be

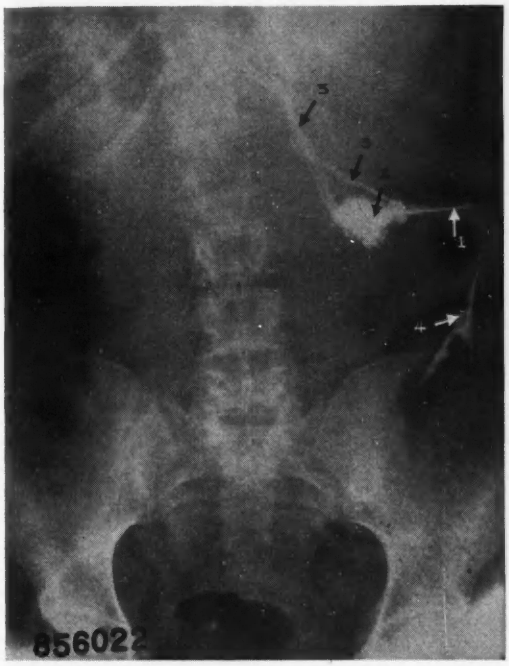

Figure 2.—Extravasation of contrast medium along the capsule of the spleen in a case of massive splenomegaly from Banti's disease. Because of this finding, the procedure was discontinued. At operation an hour and a half later, about 500 cc. of fresh blood was found in the peritoneal cavity. (1) Needle; (2) contrast medium in splenic pulp; (3) collateral circulation; (4) subcapsular contrast medium.

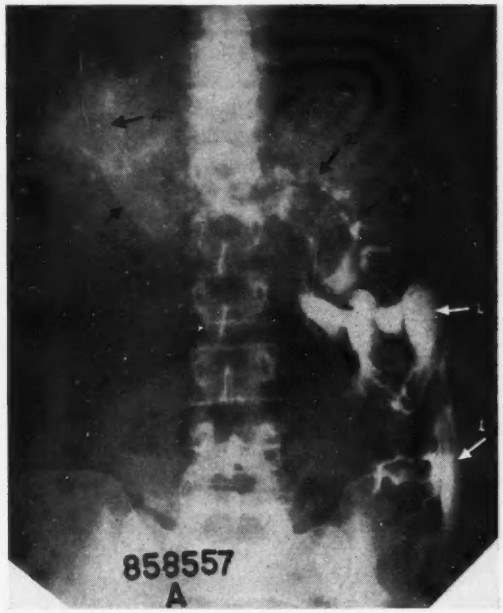

Figure 3.—Perisplenic hemorrhage following splenic puncture. The patient had cirrhosis of the liver and varices. There was also a hiatus hernia. (1) Contrast medium in peritoneal cavity and surrounding the spleen as a result of extravasation; (2) collateral circulation; (3) very poorly visualized portal vein; (4) small, atrophic liver.

possible in practically all cases. We obtained an adequate study on a child whose spleen was found to weigh 100 gm., but it would be difficult to get a needle into a child's spleen unless it were enlarged. This is also the impression of Field and Irwin[10] and many others who have done splenic puncture many times.

In all but one of our cases, hemorrhage of the splenic puncture site, when seen by the surgeon one to two hours after the injection, was found to be minimal and was considered clinically insignificant. Occasionally it was found that no blood at all had escaped into the peritoneal cavity. In one case, however, the site of needle entry was actively oozing when seen at operation an hour and a half later. About 500 cc. of blood was present in the peritoneal cavity and an 8 mm. laceration was found in the spleen, presumably owing to respiratory motion while the needle was against a rib at the time of injection. In this case films had shown reflux of contrast material from the puncture site coating the surface of the spleen (Figure 2). This condition was also observed by Leger and Proux.[13] They did not report the degree of associated splenic hemorrhage. Cooper and co-workers[7] reported a case in which some 1,000 cc. of free blood was found in the peritoneal cavity at operation. We feel that these experiences clearly point out one of the dangers of this procedure and that these hazards should be fully appreciated. It should be emphasized that in many cases in which portacaval or lienorenal shunt is contemplated there may be factors that predispose to bleeding—among them low prothrombin levels secondary to liver disease, thrombocytopenia associated with splenomegaly, and elevated portal venous pressure. Another case of splenic bleeding is shown in Figure 3.

Since splenectomy was performed immediately in all our cases, the chance of late splenic rupture from a subcapsular hematoma cannot be evaluated. This, too, may prove a definite hazard as was shown by a case reported by Walker and co-workers[22] in which the spleen had to be removed because of rupture three days after splenic puncture.

In most of the cases in our series the indication for portal venography was the need for evaluation of the anatomic features of the portal circulation in order to determine what surgical approach to use for the correction of portal hypertension. When it is necessary to decide whether a portacaval or lienorenal shunt should be done, the surgeon wishes to

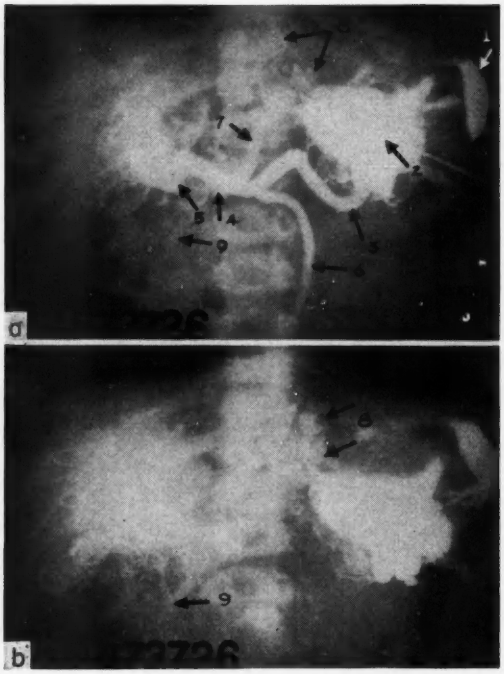

Figure 4.—Splenoportagram in a 2-year-old child with hematemesis and melena from cavernous transformation of the portal vein. *Above:* Seven seconds after injection. (1) Extracapsular contrast medium from first attempt to inject; (2) splenic pulp filled with contrast from second injection; (3) splenic vein; (4) portal vein; (5) cavernous transformation of portal vein; (6) retrograde filling of inferior mesenteric as a result of high portal pressure; (7) dilated coronary vein; (8) gastric and esophageal varices; (9) right kidney pelvis, excreting contrast from first injection. (The left was not seen, because of hydronephrosis.) *Below:* Fourteen seconds after injection. Some of the contrast has entered the veins of the liver but pronounced delay is shown.

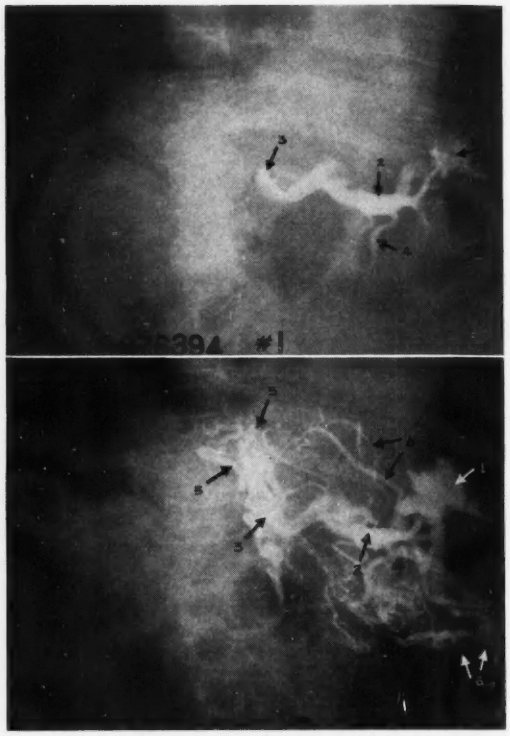

Figure 5.—Thrombosis of splenic vein. *Above:* Immediately after injection. (1) Splenic pulp; (2) dilated splenic vein; (3) obstruction at point of thrombosis; (4) retrograde filling of inferior mesenteric vein. *Below:* Same case, ten seconds after injection. No advance of the contrast can be seen in the portal vein. Note the very extensive collateral circulation. (5) Esophageal and gastric varices; (6) collateral veins.

know the size and patency of the splenic and portal veins. If an extrahepatic block exists, knowledge of its nature and location is essential. An estimation of portal pressure and the demonstration of areas of major anastomotic channels may be very helpful. Forearmed with this information, the surgeon can make a left or right-sided abdominal incision with assurance and proceed with a better conception of the problem at hand. Figure 4 demonstrates the findings in a two-year-old boy with lethargy, melena and hematemesis. The film showed an extrahepatic portal obstruction in the form of a cavernous transformation of the portal vein. Esophageal varices were also outlined. Some extravasation of contrast medium occurred. With the knowledge of the location of this extrahepatic block and that the splenic vein was sufficiently large, lienorenal shunt was carried out and the child made an uneventful recovery.

Portal venograms in cases in which portal vein thrombosis was suspected have been reported by Gvosdanovic and co-workers,[11] Cacciari and Frassinetti,[5] and Dogliotti and Abeatici.[9] Figure 5 shows a roentgenogram similar to that presented by Gvosdanovic. In this case the diagnosis was not definitely confirmed at operation, but the clinical conditions were considered typical and, since the liver biopsy showed no evidence of disease there, the portal obstruction was thought to be in the portal vein itself. Since the location of the portal obstruction as demonstrated by venography, was such as to preclude portacaval anastomosis, another approach was used.

Gastric and esophageal varices are usually opacified to show clearly—better than by barium in the esophagus (Figure 6).

Figure 6 shows the roentgenograms made after portal venography in a 14-year-old girl with hematemesis, melena and abdominal pain. The gastric and esophageal varices are well shown. The portal pressure of 37 cm. of water fell to 27 cm. after a lienorenal shunt was completed. Biopsy showed congenital cystic disease of the liver. At operation portal venography was accomplished by direct in-

jection. Cystic disease of the liver was evident (Figure 7). The films ruled out extrahepatic block, giving the surgeon added confidence in his approach. Other areas rich in vessels for anastomosis are the region of the short gastric veins and the region in and about the splenic capsule. Campi and Abeatici[6] and Dogliotti and Abeatici[9] reported successful demonstration of persistent umbilical and paraumbilical veins in cases of Cruveilhier-Baumgarten syndrome.

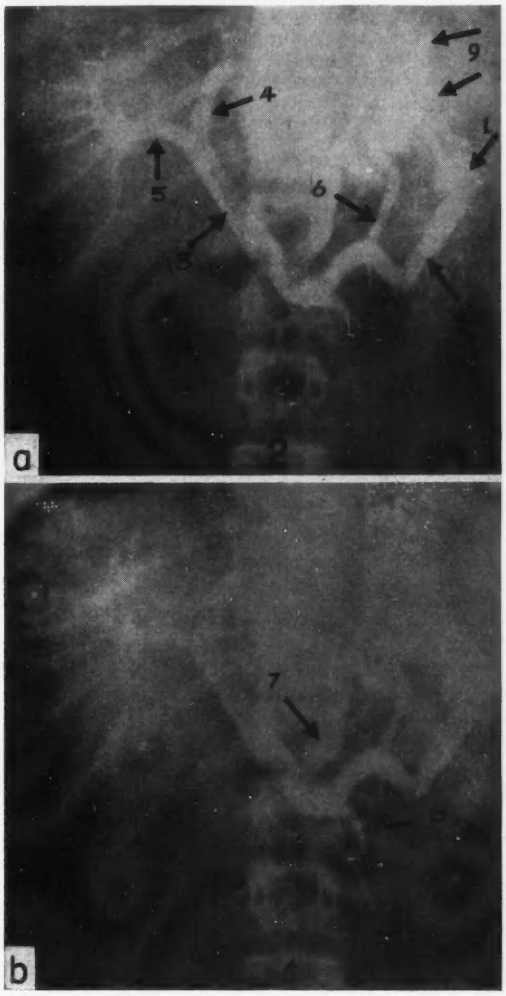

Figure 6.—Splenoportagraphy in a case of cystic disease of the liver. *Above:* Film taken four seconds after injection. *Below:* Four seconds later. The patient was one of twins, both of whom had hematemesis and enlarged spleen. (1) Splenic pulp; (2) splenic vein; (3) portal vein; (4) left hepatic branch; (5) right branch; (6) short gastric vein; (7) coronary vein; (8) retrograde filling of inferior mesenteric vein; (9) esophageal and gastric varices. The passage through the liver was slow and the branching was most unusual, suggesting some intrinsic process within the liver. The last film was not taken late enough to show opacification of liver parenchyma.

In those of our cases in which portal pressure was high at the time of operation, considerable retrograde filling of the inferior mesenteric vein was noted (Figures 4, 6). Cooper and co-workers[7] also observed this phenomenon.

Trans-splenic hepatography should be useful not only when there is question of portal obstruction, but also to study the gross structure of the liver. Figure 1 shows how well the vessels can sometimes be shown. Primary or metastatic tumors could be detected by distortion of this vascular pattern or defects in general opacification. Metastatic lesions have in fact been so diagnosed when portagrams were made by injecting the vein at operation (Moore and Bridenbaugh[15]) and also after abdominal aortography (Rigler and Olfelt[18]).

There are numerous other conditions in which splenoportagraphy is of great value. Among these are carcinoma of the body of the pancreas, pancreatic cyst, compression of the portal vein by nodes in the hepatic hilus, and various congenital anomalies, all of which have been reported by other investigators.

Department of Radiology, University of Minnesota Medical School, Minneapolis 14 (Rigler).

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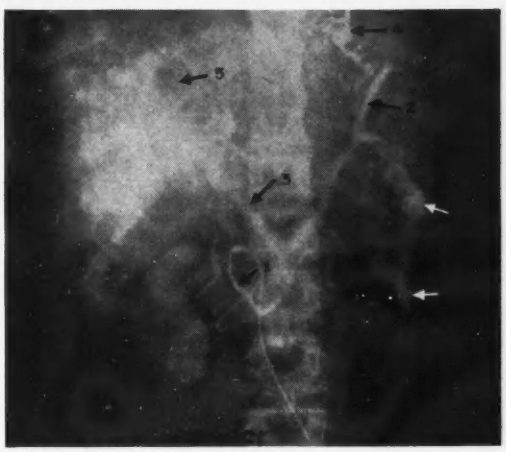

Figure 7.—Same patient as in Figure 6. Operative portal venogram. (1) Catheter in gastroepiploic vein; (2) splenic vein; (3) portal vein; (4) esophageal varices; (5) defect within opacified liver shows cystic structure, the arrow pointing to one of the larger cysts; (6) contrast excreted through kidney pelves, which are hydronephrotic.

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Splenoportagraphy in Portal Hypertension

Its Value in Selecting the Operative Procedure of Choice

WILLIAM P. MIKKELSEN, *M.D.*, and
ARTHUR C. PATTISON, *M.D.*, Los Angeles

• **Splenoportagraphy has become an almost indispensable adjunct to the surgical management of portal hypertension. In many instances it will provide the basis for the selection of the operative procedure. Certain instances of intrahepatic portal hypertension due to cirrhosis that might better be managed by splenorenal shunt rather than by the generally preferred method of direct end-to-side portacaval shunt may be determined by this procedure. The procedure finds its greatest application in the accurate delineation of the three major types of extrahepatic portal hypertension, each of which demands a different surgical approach.**

X-RAY VISUALIZATION of the portal venous system has become an almost indispensable adjunct to the surgical management of portal hypertension. Splenoportagraphy, when properly carried out, clearly delineates this system and avoids tedious and sometimes hazardous surgical dissection. Moreover, extensive surgical dissection in these cases frequently does not adequately uncover the full extent of the disease process. Splenoportagraphy, in many cases of portal hypertension, will provide the basis for the selection of the operative procedure.

Splenoportagraphy was introduced by Abeatici and Campi in 1951.[1] Their technique, as well as that of others,[3,4] involves the performance of the test in the x-ray department by means of percutaneous splenic injection of radiopaque material under local anesthetic skin infiltration.

It has been difficult for us to understand why more complications have not been reported by this technique. Early in our experience[5] we encountered significant splenic hemorrhage and now employ the procedure only in the operating room after the abdomen has been opened. This permits direct tamponade of the splenic puncture site after completion of the injection. Further, in our experience, a preoperative splenoportagram is rarely required. We do not consider this test to be of significant value in the decision as to whether or not operation is indicated. This information is obtained by the multitude of clinical features that characterize bleeding esophagogastric varices. Thus, its use is primarily for delineating the anatomical features of the portal hypertension and thus determining the operative procedure most likely to succeed. Positioning of the patient and placement of the incision are admittedly facilitated by a preoperative portagram. The lack of this information has, however, not proved a significant handicap.

The recommended initial incision is a transverse upper abdominal one that permits exploration and splenoportagraphy. The incision is then extended into the right or left chest as determined by the

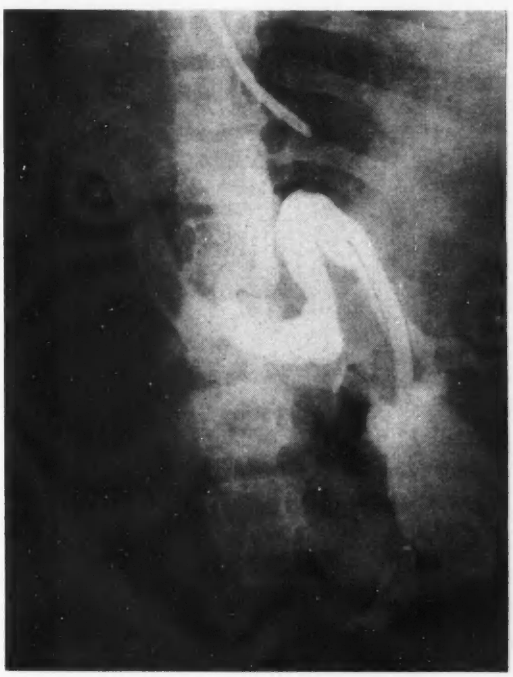

Figure 1.—Splenoportagram of 12-year-old girl with posthepatitic cirrhosis. Massive bleeding from esophagastric varices and pronounced hypersplenism were clinical features. A splenic vein, perhaps unsatisfactory for an adequate splenorenal shunt, is demonstrated.

Presented before the Section on General Surgery at the 85th Annual Session of the California Medical Association, Los Angeles, April 29 to May 2, 1956.

From the Department of Surgery, University of Southern California School of Medicine, Los Angeles 33.

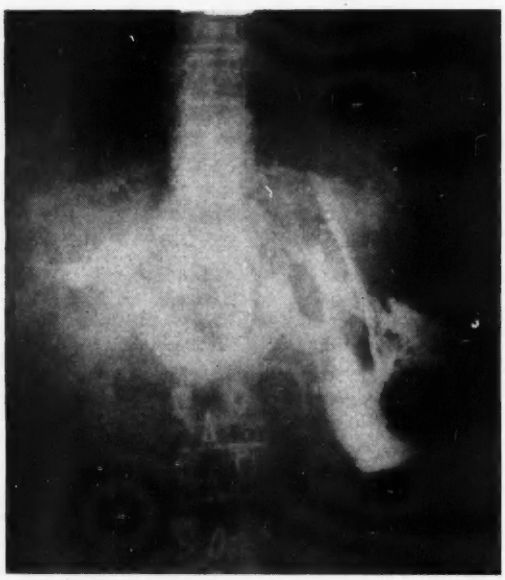

Figure 2.—Splenoportagram of 44-year-old man with posthepatitic cirrhosis. Hypersplenism was the dominant clinical manifestation. Gastrointestinal bleeding was minimal. A splenic vein suitable for splenorenal shunt is demonstrated.

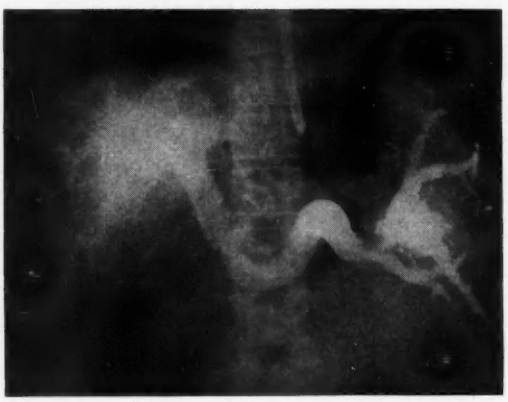

Figure 3.—Splenoportagram of 46-year-old man with posthepatitic cirrhosis. Minimal collateral circulation is noted and the finer portal radicals within the liver are clearly visualized. Complete diversion of the portal blood flow by end-to-side portacaval shunt resulted in a considerable degree of hepatic decompensation.

information obtained. In the course of this presentation, illustrative examples of the need and value of splenoportagraphy will be presented.

INTRAHEPATIC PORTAL HYPERTENSION

Although the surgical procedures designed to alleviate the complications of portal hypertension are not standardized, certain principles of such operations are generally accepted. When the primary etiologic mechanism for the portal hypertension exists within the liver and the entire portal venous tree is patent, an adequate shunt from this venous system to the caval system is the operation most likely to be of benefit. This may be accomplished by a direct portacaval shunt or by the indirect method of splenectomy and splenorenal anastomosis. The relative merits of these two operations will not be argued. Nevertheless, our experience has led us to prefer the direct portacaval shunt which we have now performed in somewhat more than 100 patients. Also we prefer to completely divide the portal vein and accomplish the shunt in an end-to-side manner. We have not employed splenoportagraphy routinely in such cirrhotic patients. Palpation of the hepatoduodenal ligament at the time of operation will usually reveal the portal vein to be taut, distended and patent. If there is any doubt in this regard there is no hesitancy to perform splenoportagraphy during operation.

Occasionally for a patient with intrahepatic portal hypertension who has a patent portal venous tree, a splenorenal anastomosis will be preferred. This situation is encountered when significant hypersplenism as manifested by severe pancytopenia is present and splenectomy would seem desirable. In many such situations, however, it must be recognized that relief of the hypersplenism will occur when portal decompression is accomplished by direct portacaval anastomosis even though the spleen is not removed. The efficiency of a venous shunt in eliminating portal hypertension depends to a great extent upon the size of the afferent vessel and the size of the anastomosis. Thus, in choosing a splenorenal anastomosis over a direct portacaval anastomosis, it is essential that the splenic vein be of appropriate size. Usually the primary purpose of these operations is to alleviate the threat of life-endangering hemorrhage from esophagogastric varices. One must thus weigh carefully these two factors when dealing with a patient with intrahepatic portal hypertension and hypersplenism.

This problem is exemplified by a brief account of two representative patients. In both patients severe pancytopenia secondary to intrahepatic portal hypertension, due to cirrhosis was manifest. The first patient was a 12-year-old girl who had bled massively on two occasions within three weeks preceding operation. Pronounced leukopenia and thrombocytopenia were present. Upon examination of the splenoportagram it was noted that the splenic hilar veins did not fuse to form the common splenic vein for quite a distance from the spleen (Figure 1). This suggested there might be difficulty dissecting out a sufficiently large splenic vein for anastomosis and hence the possibility that a graft might

be required. In our opinion, available autogenous grafts are not of sufficient diameter to guarantee a satisfactory shunt. Our primary concern with this patient was to relieve the portal hypertension and control the bleeding. Thus a direct portacaval shunt was performed and the portal pressure was reduced to a normal range. In five months of observation after operation she had no further bleeding and the depression in circulating cellular elements steadily improved but had not yet risen to normal levels at the time of last observation.

The second patient was a 44-year-old man who also had pronounced pancytopenia and thrombocytopenia. Gastrointestinal bleeding had occurred but had never been massive. A splenoportagram (Figure 2) showed a large splenic vein, eminently suitable for anastomosis. Of major concern in this patient was the control of hypersplenism. A splenectomy followed by splenorenal shunt was decided upon. A rather poor reduction in portal pressure was obtained. The circulating cellular elements returned immediately to normal levels, where they remained. There was no further gastrointestinal bleeding.

Another way in which splenoportagraphic delineation may help in surgical consideration of a case of intrahepatic portal hypertension is in estimating the amount of blood flow through the liver that is contributed by the portal vein. In the usual cirrhotic patient, the total liver blood flow is reduced about 50 per cent. This occurs in spite of the apparent pronounced increase in arterial blood that reaches the liver. The assumption is that reduction in flow of blood through the liver takes place primarily at the expense of the portal flow. It is reasonable to believe that rather significant differences may exist in this regard from one cirrhotic patient to another. If it could be determined beforehand that one was dealing with the unusual cirrhotic patient whose portal vein was contributing the majority of liver blood flow, the surgeon might be reluctant to completely divert this flow from the liver as is done in an end-to-side portacaval shunt.

When a splenoportagram fails to show significant collateral vessels and the finer portal radicals within the liver are clearly visualized, it is a justifiable interpretation that portal flow is rapid and liver obstruction is minimal. It may further be deduced in such a situation that the portal vein is contributing a significant amount of the total flow of blood through the liver. A preoperative indication that this problem may exist is presented when an esophagram or esophagoscopy fails to reveal significant varices in a cirrhotic patient who has bled. We now perform splenoportagraphy routinely in these patients and utilize splenorenal anastomosis if our preoperative suspicions are confirmed. Figure 3 is a splenoportagram in the case of such a patient, in whom a direct end-to-side portacaval shunt was done. Preoperative evaluation indicated this patient to be an excellent surgical candidate. The postoperative course was uneventful for two weeks and the patient was discharged from the hospital. He returned two weeks later with icterus and ascites. Liver function studies demonstrated significant impairment, much greater than might be anticipated from the effects of anesthetic and sur-

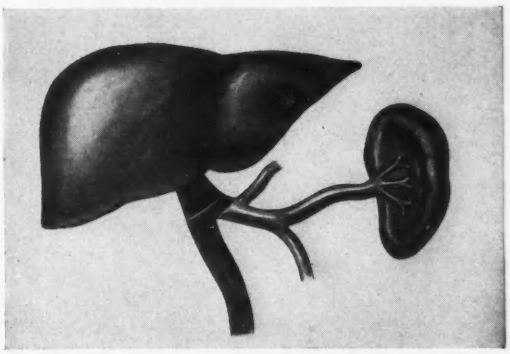

Figure 4.—Extrahepatic portal hypertension: Type No. 1. The portal vein alone or the portal and superior mesenteric veins are occluded. The splenic and coronary veins are patent.

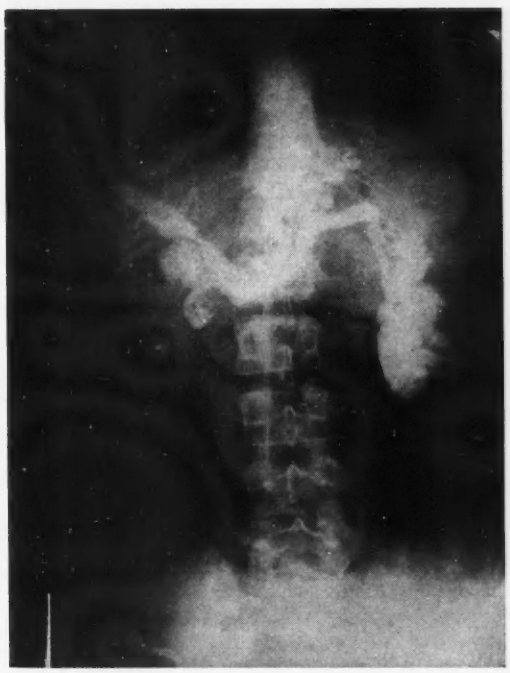

Figure 5.—Splenoportagram of 34-year-old man with decided narrowing of the portal vein due to chronic pancreatitis localized to the head of the gland.

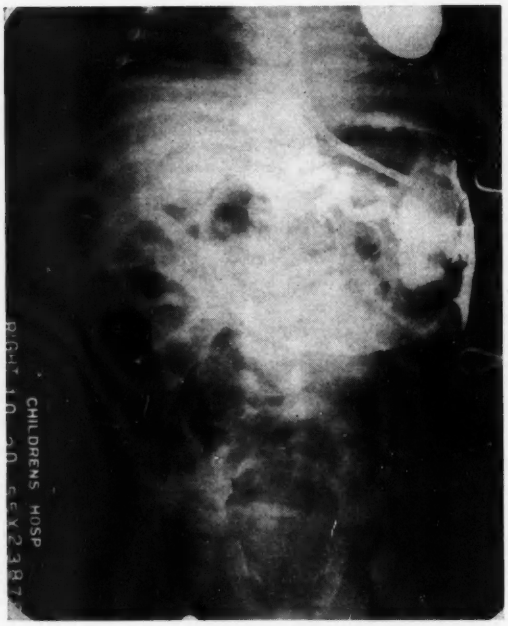

Figure 6.—Splenoportagram of nine-months-old infant. Neither the portal nor the superior mesenteric vein is visualized. A large coronary vein is apparent.

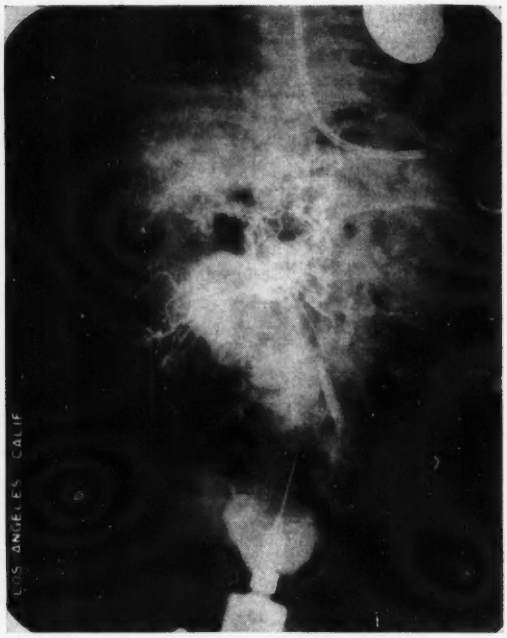

Figure 7.—Jejunal portagram in same infant as shown in Figure 6. Complete obliteration of both the portal and superior mesenteric veins is confirmed.

gical stress alone. The subsequent course was a slow but definite improvement. Perhaps in this patient this degree of hepatic decompensation would not have developed if splenorenal shunt had been done.

EXTRAHEPATIC PORTAL HYPERTENSION

Splenoportagraphy, though valuable in cirrhosis, finds its greatest use in delineation of the disease process in extrahepatic portal hypertension. In this disease, the pathologic process involves obstruction of the portal vein or one or more of its tributaries. The liver itself is normal. The site and extent of this venous obstructive process will determine the surgical approach. Although there are minor anatomical variations in the portal venous tree, from a therapeutic standpoint three significant variations of extrahepatic portal hypertension are encountered. For the sake of convenience, we have elected to label these as types 1, 2, and 3. Minor variations of these types will occasionally be encountered.

Type 1 (Figure 4): The portal vein alone or the portal and superior mesenteric veins are occluded. The splenic and coronary veins are patent. All of the splanchnic return blood flow is shunted to the caval system via inadequate collaterals. In this instance a direct portacaval shunt is impossible. A splenorenal shunt for this problem is the procedure most likely to result in decompression of the esophagogastric varices. Shunts using the superior

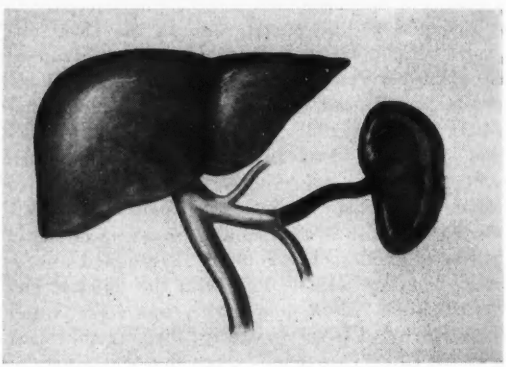

Figure 8.—Extrahepatic portal hypertension: Type No. 2. The splenic vein alone is thrombosed. The portal and superior mesenteric veins are patent.

mesenteric vein here, are unlikely to succeed since only the intestinal veins drained by this vessel will be decompressed. No relief will be afforded the venous return from the spleen, stomach or left colon.

Figure 5 is a splenoportagram taken in the case of a 34-year-old man with gastrointestinal bleeding and splenomegaly. The pronounced narrowing in the portal vein was due to chronic pancreatitis localized to the head of the gland. Splenorenal anastomosis successfully relieved the gastrointestinal bleeding.

Figure 6 is a splenoportagram in the case of a

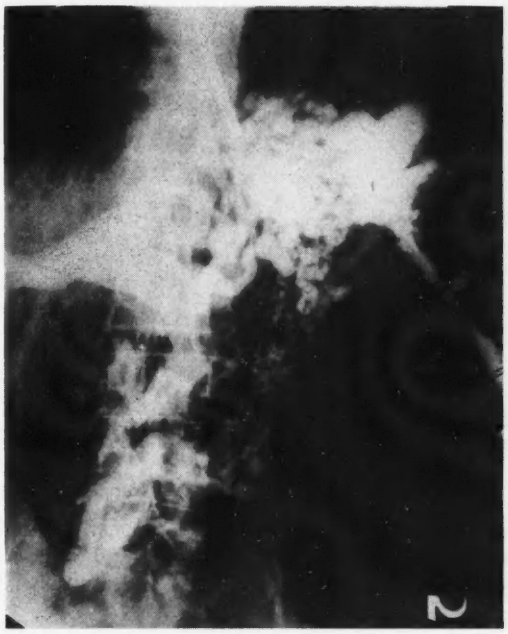

Figure 9.—Splenoportagram of 56-year-old man. A huge collateral circumvents the splenic vein obstruction to outline normally patent superior mesenteric and portal veins.

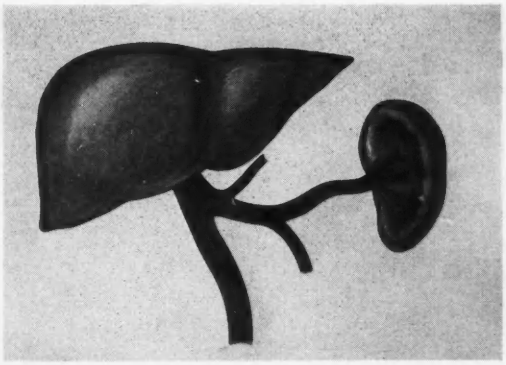

Figure 10.—Extrahepatic portal hypertension: Type No. 3. The major veins of the entire portal system are thrombosed.

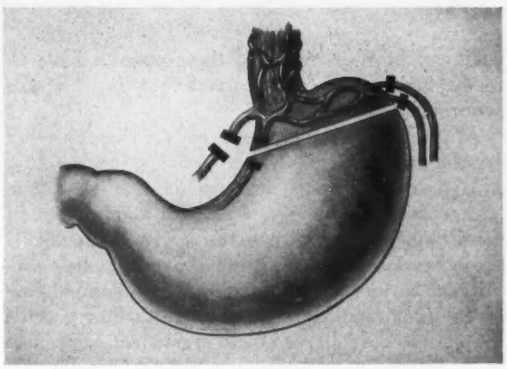

Figure 11.—Diagrammatic presentation of portal-azygos disconnection by division and immediate resuture of the gastric cardia.

nine-month-old infant, with thrombosis of both the portal and superior mesenteric veins which was secondary to omphalitis following birth. Splenorenal shunt was successfully carried out. When the initial splenoportagram shows obstruction in the splenic vein, as it did in this infant, it is essential to perform a secondary portagram (Figure 7) via a jejunal mesenteric vein. This procedure is required to ascertain the status of the superior mesenteric and portal veins. If the splenic vein alone is obstructed, a lesser operative procedure is indicated. This will be clarified in succeeding paragraphs.

Type 2 (Figure 8): The splenic vein alone is thrombosed. In cases of this type the venous return from the majority of the abdominal viscera is flowing unobstructed in a normal fashion through the superior mesenteric and portal veins. The venous return from the spleen and perhaps part of the stomach is the only segment obstructed. In this situation, splenectomy alone, will suffice. The contribution of splenic blood to the varices, here, is probably in the neighborhood of 80 per cent or more. Figure 9 is a splenoportagram in the case of a 56-year-old man who had severe bleeding from varices. It was noted that a greatly enlarged collateral vessel circumvented the splenic vein obstruction to outline normally patent superior mesenteric and portal veins. This extensive collateral, however, had included the azygos and hemi-azygos systems in the mediastinum, resulting in esophagogastric varices. The etiologic process was a pseudocyst of the tail of the pancreas. No further bleeding occurred after splenectomy and distal pancreatectomy was carried out.

Type 3 (Figure 10): The major veins of the portal system are all thrombosed. No type of veno-venous shunt is possible in this situation. Shunts have been attempted between rather large collateral veins and the caval system, but they have failed since only a small segment of the splanchnic venous return was thus decompressed. In extrahepatic portal hypertension of this type it is necessary to operate directly on the varices. Three methods, each with minor variations, are available to accomplish this. The efficacy of each has yet to be determined. The three methods are segmental esophagogastrectomy, transesophageal ligation of the varices and portal azygos disconnection by transsection and resuture of the gastric cardia. Splenectomy may or may not be done as an adjunct to any of these pro-

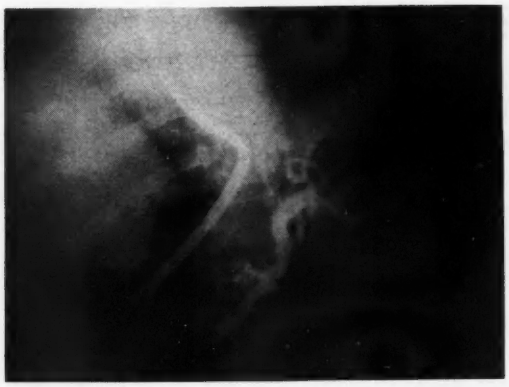

Figure 12.—Splenoportagram of 62-year-old woman. None of the major tributaries of the portal circulation are visualized. The one significant vein seen is the gastro-epiploic.

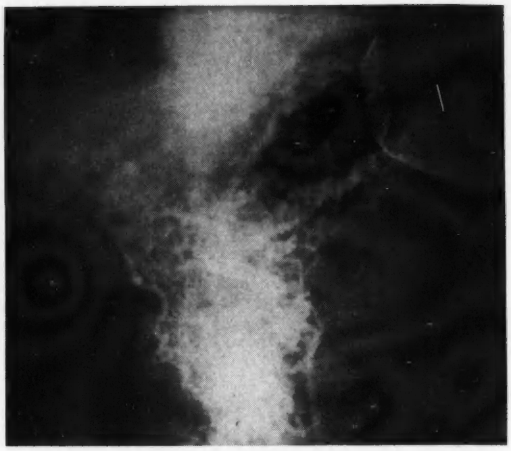

Figure 13.—Jejunal portagram of same patient shown in Figure 11. Neither the superior mesenteric nor the portal vein is visualized.

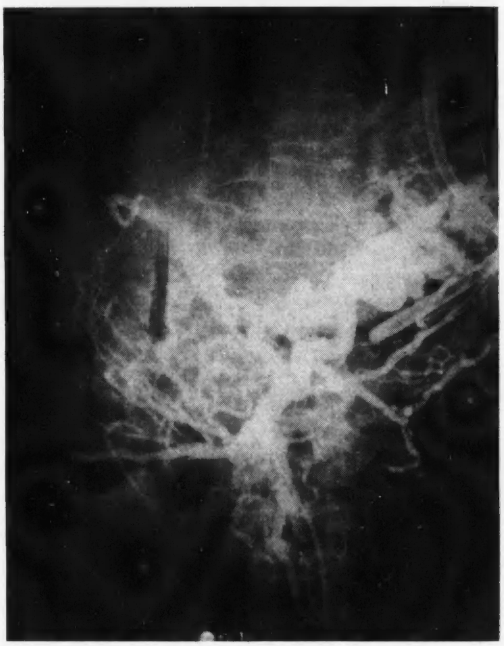

Figure 14.—Jejunal portagram of patient who had post-splenectomy bleeding. Collateral by-passing obliteration of portal, splenic and superior mesenteric veins is demonstrated.

cedures. However, many of these patients have already had splenectomy carried out for "Banti's syndrome."

At present we prefer portal azygos disconnection for the management of these patients (Figure 11). This procedure would seem to offer at least temporary control of the varices with a minimum of disturbing postoperative sequelae. The rationale of the operation stems from the recognition that esophageal varices are filled from the abdominal side of the diaphragm. Interruption of this flow permits the varices to collapse. How permanent this effect will be remains to be ascertained. Pyloroplasty is required as an adjunct to this procedure in order to permit adequate gastric drainage, since vagotomy is technically unavoidable. Fortunately, vagotomy is desirable, since it interrupts the cephalic phase of gastric secretion and reduces the acid secretion of the stomach. Pyloroplasty accomplishes a similar result by reducing the antral phase of gastric secretion. It is believed by many observers that acid-peptic erosion of the esophageal mucosa is the initiating factor in varix bleeding. Our experience with this procedure is limited to two recent satisfactory results. In a recent personal communication, Mr. N. C. Tanner of St. James Hospital, London, stated that he is observing eight patients who have had this operation. None has bled and none has significant gastrointestinal complaints. The longest period of follow-up in this series is four years. It is readily apparent that further appraisal of this procedure is required.

Our preference for portal azygos disconnection has developed from dissatisfaction with the first two procedures listed. In three of four patients we operated upon, segmental esophagogastrectomy was followed by disabling esophagitis. Perhaps a more extensive proximal gastrectomy would offer greater protection in this regard. This operation, however, is a major one and a significantly higher operative mortality must be anticipated.

We have performed transesophageal ligation of varices in five patients. Three bled significantly after operation and two are now dead. The remaining two did not have further bleeding and were doing

satisfactorily when last observed, one of them 19 months and the other 27 months after operation. One of them had vagotomy, pyloroplasty and splenectomy in addition to ligation of the varices.

Figure 12 is a splenoportagram of this patient. The rather large vein leading from the spleen is not the splenic vein but rather the gastroepiploic vein. That the entire major portal system is obstructed is apparent in Figure 13, a portagram made with a jejunal mesenteric vein utilized for the injection. Pronounced collateral development without patency of the superior mesenteric or portal veins is demonstrated.

A similar picture of complete occlusion of all of the major radicals of the portal system is seen in Figure 14. The patient had had splenectomy four years previously for "Banti's syndrome." This portagram was obtained via a jejunal mesenteric vein.

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Subclinical Epileptic Seizures

Impairment of Motor Performance and Derivative Difficulties

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• **Modern clinical observations have greatly expanded the conception of the characteristics of the various kinds of epilepsy. By simultaneously recording electroencephalograms and the performance of simple motor tasks, it has been possible to demonstrate the effects of epileptic seizures not detectable by unaided observation and not noted by the patient. The effects of these subclinical seizures have been manifested variously—by a lengthening of the time between stimulus and reaction, by inaccuracies of response to stimuli, or by total cessation of performance.**

From this study it is suggested that subclinical seizures probably play a role in producing some of the psychiatric conditions associated with the convulsive disorders, as well as primary behavior disturbances and undifferentiated mental deficiency. It is also suggested that such subclinical seizures may possibly contribute to the characteristics of some cases of criminality and antisocial reactions and schizophrenic reactions.

THE PURPOSE OF THIS PAPER is to present evidence that subclinical epileptic seizures may impair simple motor performance and to point out possible relationships of such impairment to more complex performance and ultimately to disturbed clinical behavior.

It is now well established that in focal seizures every gradation of impairment of consciousness may occur, from none at all to total loss of awareness. Symptoms of seizures are myriad and may include an almost limitless variety of involuntary motor acts, false sensory experiences and affective changes. In conjunction with the method used in the present study, it may be well to note at this point that, in some partial seizures, awareness of various sensory stimuli continues but the capacity to respond to them is lost. For example, it is not unusual for some patients with seizures, especially of the temporal lobe variety, to recall that they have been able to hear and understand the speech of others after they had lost the ability to respond to it.

By studies reported in 1941 and 1947, Schwab[18,19] opened new ways to study the effects of seizures on individuals. He tested the ability of patients with petit mal seizures to make motor responses to auditory and visual stimuli during attacks. Stimuli and responses were recorded simultaneously with the electroencephalograph so that the temporal relationship of each to the others could be ascertained. It was found that always if there was any response at all to a stimulus given during a seizure burst, the reaction time—that is, the interval between the stimulus and the response—was longer than it was to the same stimuli at other times. Degrees of prolongation varied roughly in proportion to the length of the seizure bursts as seen in the electroencephalograph; and often with the longer bursts there was no response to the stimuli. Schwab concluded that he had demonstrated six degrees of impairment of consciousness as reflected in the various degrees of prolongation of reaction times. Although Schwab did not say so, it would appear from the brevity of some of the bursts noted and the minimal effect they had upon the reaction time, that many of the seizures recorded would not have been detectable by ordinary clinical observations.

In 1953, Bates[1] reported the use of an apparently independent but similar technique in the study of a single case of petit mal epilepsy. By making synchronous recordings of electroencephalographic and sound impulses while the patient was reading, he demonstrated various degrees of impaired consciousness.

In the present study an apparatus like Schwab's was used, and the technique was somewhat similar. However, the effects of subclinical seizures upon spontaneously sustained performance were noted, as well as responses to stimuli. The present study also dealt with seizures other than petit mal lapses. Moreover, subclinical seizures were correlated with alterations of performance other than and in addition to the prolongation of reaction time. A final point on which the present study differed from Schwab's was that attention was given to the psychiatric implications of the effects of such seizures.

Figure 1 illustrates the technique employed in this study. The patient was prepared for a routine electroencephalograph which was recorded on the channels shown. A small magnet was attached to one

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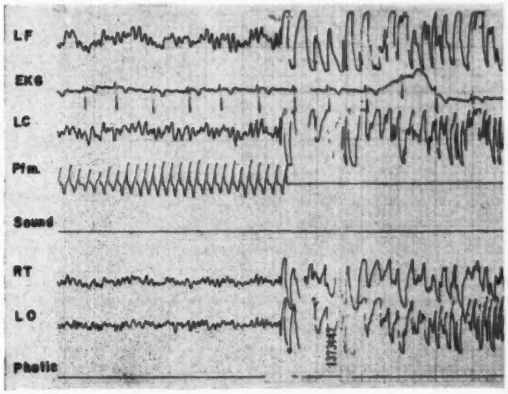

Figure 1.—Cessation of performance with grand mal seizure.

finger and a stationary induction coil was placed just in front of the magnet so that movements of the finger set up potentials in the coil, which were recorded on one channel of the electroencephalograph.* The patient was instructed to tap his finger at any rate he chose. As can be seen, the task was being performed steadily and rhythmically until shortly after the onset of an extremely high amplitude paroxysmal discharge, like that of grand mal seizure, which was inadvertently precipitated by intravenous injection of metrazol. When this occurred, finger movement stopped entirely.

Similarly, Figure 2 shows a total cessation of performance during a petit mal lapse. In this record the patient was responding to sound stimuli recorded by way of a microphone on another channel of the electroencephalograph.†

Figure 3 presents the first example of what is here referred to as subclinical seizures. The patient was a 15-year-old boy with a diagnosis of "primary behavior reaction." He has never been known to have had any form of seizure. Symptoms had consisted essentially of shy, withdrawn behavior and difficulty in learning. The figure shows a total cessation of spontaneously sustained performance associated with a burst of paroxysmal theta activity on the electroencephalograph. It will be noted that at the termination of the paroxysm, performance was resumed. The patient was unaware that he had stopped. This patient showed numerous such bursts with impaired performance, but at no time was there a clinically observable seizure.

*Reference may be made to a technical note made by Lipton[15] for a detailed description of this portion of the apparatus.

†When light was used as a stimulus it was recorded by means of a photoelectric cell through a channel of the electroencephalograph.

KEY TO ABBREVIATIONS ON MARGINS OF ILLUSTRATIONS

LF = Left frontal
RF = Right frontal
LC = Left central
RC = Right central
LT = Left temporal
RT = Right temporal
LO = Left occipital
RO = Right occipital
LP = Left parietal
RP = Right parietal
Photic = Stimulus by light
Sound = Stimulus by sound
Pfm = Performance

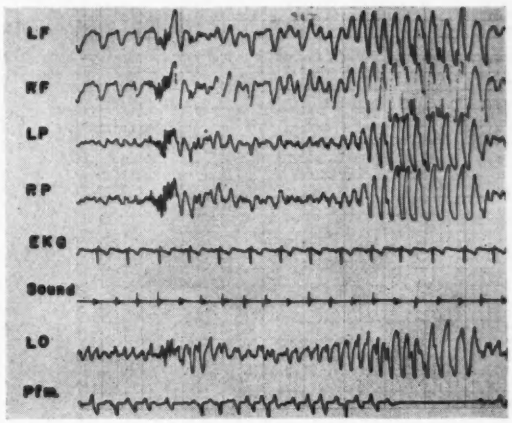

Figure 2.—Cessation of performance with petit mal seizure.

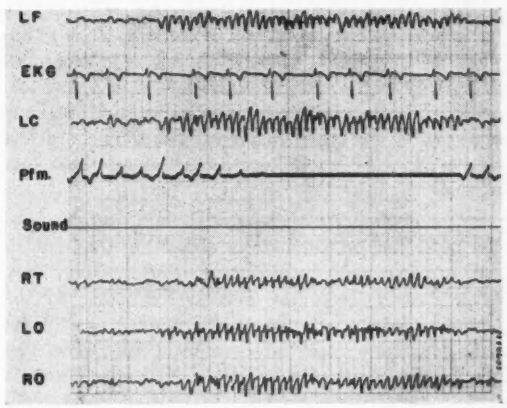

Figure 3.—Cessation of performance without clinical seizure.

The present study grew out of an interest in the high incidence of abnormal electroencephalographic tracing, particularly the paroxysmal type, in children and adolescents with clinical evidence of a primary behavior disorder. That such electroencephalographic abnormalities are common is well supported by a number of studies,[2,3,10,14] beginning with that of Jasper, Solomon and Bradley[12] in 1938, although not every such study has demonstrated similar findings.[5] The relationship, however, of the electrical changes to disturbances of behavior is not known. That is to say, even after the discovery of an abnormality in

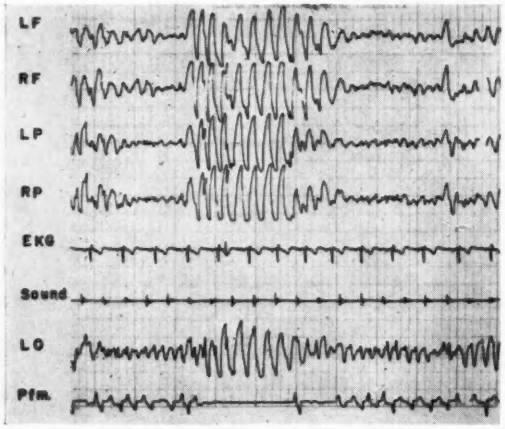

Figure 4.—Cessation of performance without clinical seizure.

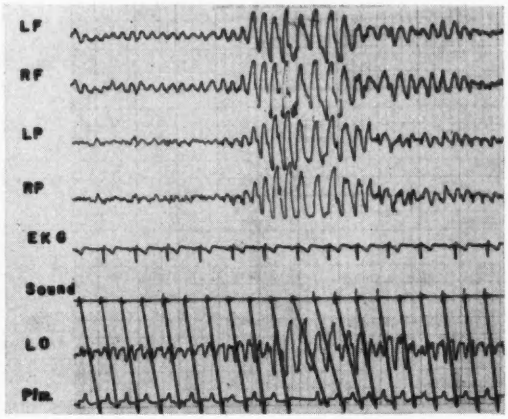

Figure 5.—Delay in response to stimuli.

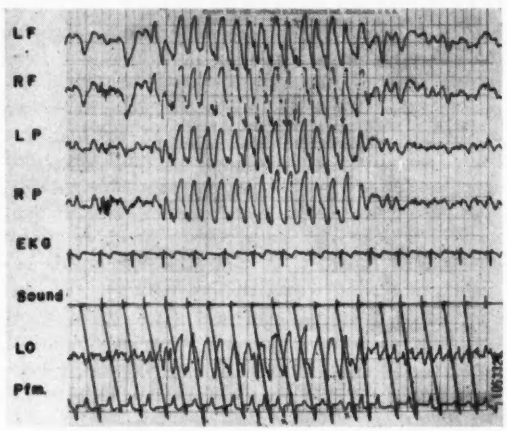

Figure 6.—Performance in excess of number of stimuli.

the electroencephalogram in a given case, it is impossible to evaluate what influence the abnormality is having on the clinical condition. One seems justified in entertaining the possibility that patients could show disturbed behavior, either as the direct effects of, or as psychological reactions to these subclinical seizures.

Some comment with respect to the location of the electrical foci in such cases seems pertinent. Such foci are extremely variable in location. They may arise directly from the cortex, frequently of the temporal lobe; the subcortical regions, chiefly the rhinencephalon; and the centrencephalic area, primarily the diencephalon. The intercommunicating systems which are referred to as cortico-thalamic sectors are significant in the mediation of the clinical manifestations of such seizures. In the case of the 15-year-old boy previously discussed, it was not possible from the record obtained to definitely localize the discharge more than to say that the paroxysmal bursts were of the type that are often associated with psychomotor automatisms, many of which are centrencephalic in origin.

In connection with one of these systems, namely the temporo-thalamic sector, it may be recalled that Hughlings Jackson recognized that uncinate fits frequently had affective components. More recently the report by Davidoff,[4] among others, showed that affectively charged ideas can occur as substantially the only symptoms in some temporal lobe seizures. Gibbs and co-workers[8,9] emphasized that the incidence of various psychiatric syndromes, including psychoses, psychoneuroses and severe personality disturbances is very high in persons with temporal lobe epilepsy. They also noted that the longer the interval between seizures the greater the emotional disturbances were likely to be. Conversely, the occurrence of frequent seizures tended to be accompanied by a reduction in the emotional disturbances. These observations were strongly supported by the studies of Ostow,[16] of Scott and Masland[20] and of Ervin and co-workers[6] (the last mentioned of whom included especially thorough psychological and psychiatric evaluations of their patients).

Until an adequate series is studied, it remains only a conjecture, but still a good possibility, that subclinical seizures in a patient of this type may be directly affecting the apparatus of emotions which the work of Penfield[21] showed to be activated by electrical stimulation of diseased temporal lobe cortices.

Figure 4 shows total cessation of performance associated with a paroxysmal burst not accompanied by a seizure detectable by ordinary observation. This graph was taken from the electroencephalogram of a young woman who had frequent clinical petit mal seizures.

Figure 5 shows a frequently encountered change in performance associated with paroxysmal bursts. Lines have been drawn between the stimulus and response pips.‡ In this case a delay in response (prolonged reaction time of Schwab) resulted, although the patient continued accurately to give one response to each stimulus.

Figure 6 shows still another type of change in performance often seen with a subclinical seizure. Again lines have been drawn from the stimulus to the response pips. During a burst, three responses appeared in excess of the number of stimuli, whereas, in the absence of the paroxysmal activity, responses were accurate.

Figure 7 is shown to illustrate the relative accuracy of response which some individuals maintain during highly abnormal electroencephalographic activity. The patient was a 16-year-old boy who had idiopathic grand mal and petit mal seizures and whose electroencephalographic record shows the sort of severely abnormal activity evident in the figure shown, virtually all the time. Again lines have been drawn between the stimulus pips and response pips and although the rate of the stimulation was being varied at random, the patient responded to all but two stimuli. During this time the electroencephalogram was severely abnormal, showing high amplitude, slow, as well as spike and slow wave activity. It will be noted that at the point at which he missed two responses, the spiking activity had become predominant, which is in accord with an observation made by Schwab. It is interesting to speculate upon the possibility that over the long course of his severe disturbance the patient had learned to partially compensate for the accompanying impairment of function so that by the time the tracing shown in Figure 7 was made, he could perform accurately in the presence of bursts which earlier would have disabled him.

Although this patient showed largely accurate responses in this particular illustration, at other times he showed marked impairment of performance with subclinical seizures. In connection with this observation a segment of his history is pertinent. He had seemed normal and vigorous both mentally and physically until the onset of his convulsive disorder four years previously. Shortly after the onset of the illness, his intelligence quotient was 98. After four years of frequent convulsions, his intelligence quotient was 48 and his intellectual functioning was at the moron level. There is no doubt that Gastaut[7] expressed a current and widely accepted point of view when he remarked that impairment of intellectual functions in epilepsy results only from the brain lesions causing the epilepsy and not from the seizures per se. Idiopathic epilepsy is held never to cause such impairment. It occurs to the authors of this paper that the patient here under consideration had "deteriorated," probably on the basis of frequent—almost constant—subclinical seizures.* We cannot assert positively, of course, that he had no structural brain disorder, but careful clinical investigation, including pneumoencephalograms, failed to reveal any. It is thus suggested that in this patient deterioration was an ictus phenomenon consisting chiefly of subclinical seizures.

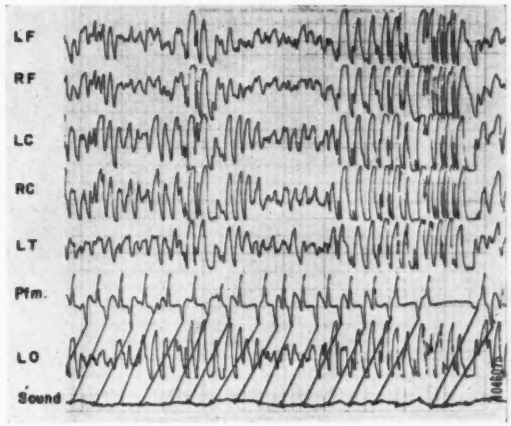

Figure 7.—Performance during constant paroxysmal activity.

The term *deterioration* is used in one sense as meaning organic degeneration, which probably does not occur in a case of this type. In another sense, apparent deterioration may be conceived of as occurring in either or both of two ways. The first would result from the taking over of facilitated pathways by a discharge which introduces patterns of positive but distorted perceptions through which memory patterns, which are not related to afferent stimuli, are called up. Examples of distortion of this kind are "forced thinking," delusional or hallucinatory experiences, anxieties, hysterical manifestations, or even schizophrenic reactions.

The second way "deterioration" might occur is by the interruption of normally functioning memory or thought events by the paroxysmal discharges which interfere with the natural continuity of thought sequences. The type of thought distortion will depend upon the area of interruption. In the light of this concept, one might conjecture that the level of intellectual functioning could be noticeably reduced by the simple but repetitive interruption of logical, unified thought sequences essential to reasoning. The intellectual deterioration noted in the present case could be explained in this way.

‡The term *pips* is applied to the pinnacles or nadirs in tracings which indicate the extremes of action that is being recorded.

*He has clinical seizures too, but no one has ever contended that intellectual functioning was unimpaired during clinical seizures of a major type.

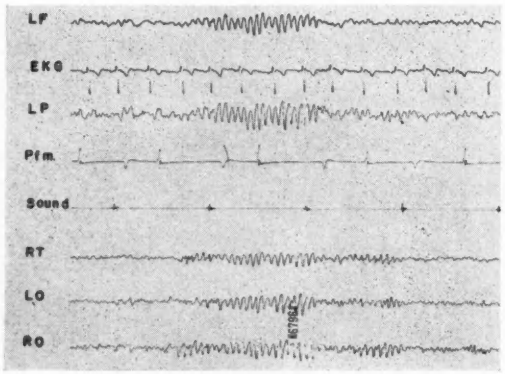

Figure 8.—No alteration of performance.

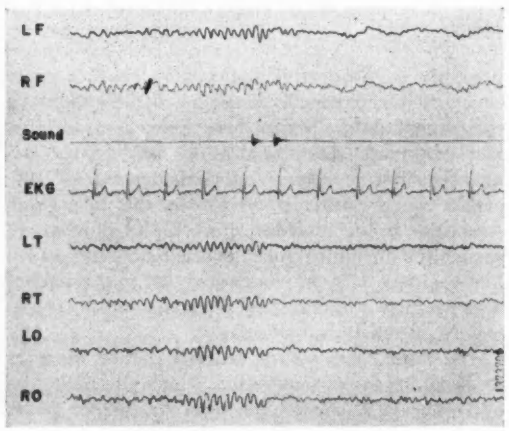

Figure 9.—Suppression of paroxysmal burst.

Figure 8 is taken from the record of the same patient as Figure 3 and is presented to show that sometimes (but uncommonly) no change in performance is detected even with the appearance of a clear-cut paroxysmal burst. In this case two stimuli occurred during the burst and no alteration of response was noted. It seems reasonable to expect that by varying the complexity of the performance response, precise measurements of degrees of impairment might be made. It appears probable that delays in responses and inaccurate (missed and extra) responses are owing to intermediate degrees of impairment between none at all and impairment so severe as to cause total cessation of performance. Specifically, it should be expected that with lesser degrees of impairment more complex responses could be executed without error, and with greater impairment more errors would be evident with increasing complexity of the performance task. Thus it is possible that this patient, who performed well as tested, might have shown impairment if he had been responding to more rapid stimulation or, for example, had been asked to respond to alternate stimuli rather than to consecutive ones.

Conversely, some preservation of the ability to do deliberate acts might possibly be demonstrated in some of the patients who showed complete cessation of response, provided that an even simpler test than movement of a finger could be devised. Finally, in order to test more fully the total reaction or response of a person, the simple motor output must be equated with functional disturbances that appear in response to discharges in other areas of the brain which have only remote influence or none at all upon the motor systems. Further research is being directed toward such problems.

Figure 9 is shown simply to illustrate one of the technical difficulties which may occur in testing of this type. It shows a paroxysm being suppressed in response to auditory stimulation. Such suppression as this has been described previously by Schwab and others.

There are certain limitations to this method. As was just shown, it cannot be used to study the effects of activity which it suppresses. Application to extremely brief, transient activity is also difficult. Finally, of course, it can be used only with patients able and willing to cooperate.

Another limiting factor is that only motor responses are recorded and, as suggested earlier, ability to make such responses may not be impaired unless some influence is brought to bear upon the motor systems. This method does not test for all possible effects of subclinical seizures and some may take forms which cannot be studied in this way. In those cases, other techniques for studying cerebral dysfunction will have to be devised.

Three other clinical groups for which we do not have illustrative material should be mentioned. As recently shown by Walter, Yeager and Rubin,[21] paroxysmal activity is found in an enormously high proportion of patients with undifferentiated mental deficiency. Hill[11] and others have shown similar but less pronounced changes in psychopathic and criminal persons. Much less decided changes have been reported by a number of investigators, most recently Kennard,[13] in schizophrenia. The possibility that subclinical seizures contribute to the impaired intellectual functioning of such mental defectives is certainly an excellent one, and some role in the other clinical groups mentioned seems possible.

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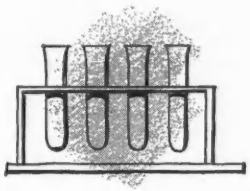

Vitamin D Resistant Rickets

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• **Vitamin D resistant rickets is not a rare disorder. Increased awareness of this metabolic disorder during the examination of children with bowed legs, even infants receiving normal supplements of vitamin D, may lead to diagnosis oftener. Ten previously unrecorded cases of this disorder are included within this report. Three of the patients had associated congenital anomalies which also required treatment. Treatment of the vitamin D resistant rickets consists of the oral administration of large doses of vitamin D. Careful observation of patients during vitamin D therapy to prevent overdosage and resultant hypercalcemia is of utmost importance.**

Surgical correction of the bony deformities is rarely necessary.

The cause of vitamin D resistant rickets is thought to be a defect of renal tubular mechanisms.

THE SYNDROME of rickets resistant to normal therapeutic doses of vitamin D but amenable to massive doses was first described by Albright, Butler and Bloomberg in 1927.[1,2] Until 1950, the number of known cases was approximately 30,[11] but increased awareness of this entity has brought the total of reported cases to over 75.[13,18,21,24,25] The authors' experience with ten cases will be reviewed with emphasis on the clinical features, pathogenesis, differential diagnosis, treatment and associated congenital anomalies (Chart 1).

REPORTS OF CASES

CASE 1. The patient was noted by her parents to have "peculiar legs" from birth. Bowing of the legs became increasingly evident when she began to walk, in spite of persistent orthopedic measures. At the age of three and a half years, she was sent to the U.C.L.A. Pediatric Clinic with a tentative diagnosis of rickets resistant to vitamin D. Dietary history was normal, including 1,000 to 2,000 units of vitamin D in a water-miscible vehicle daily since birth. Upon physical examination, moderate bowing of all leg bones, and moderate enlargement of the costochondral junctions and wrists were noted. In addition, the shape of the skull was quite unusual; although the circumference was normal, the head appeared narrow and elongated. Examination of the ocular fundi by an ophthalmologist confirmed the presence of papilledema. Both eyes appeared unduly prominent. Roentgen studies of the long bones showed bowing, hypomineralization and cupping, fraying and spreading of metaphyses. Numerous views of the skull provided radiological evidence of premature closure of the sagittal cranial suture (or overmineralization). The blood calcium was within the normal range, the phosphorus content 2.6 mg. per 100 cc., and alkaline phosphatase slightly above the normal range. No abnormalities of fat absorption, acidosis or gross renal function could be demonstrated. Amino-aciduria was demonstrated by paper chromatography. Excretion of beta amino isobutyric acid, methyl histidine, glycine and serine was especially high.

A diagnosis of vitamin D resistant rickets and premature closure of the cranial sutures was made. Surgical treatment of the skull resulted in relief of papilledema. Vitamin D administration in dosages ranging from 50,000 to 150,000 units a day resulted in pronounced improvement in the rachitic lesions, as well as decreased amino-aciduria.

CASE 2. A girl was referred to the U.C.L.A. Pediatric Clinic at two years of age for evaluation of bowed legs. She had received normal amounts of vitamin D since she was two weeks of age. X-ray studies of the lower extremities showed changes typical of rickets. Results of urinalysis were normal. The blood calcium level was 10.6 mg. per 100 cc., phosphorus 3.0 mg. per 100 cc., and alkaline phosphatase 35 King-Armstrong units. Blood urea nitrogen, bicarbonate content and chloride content were within normal limits. Intravenous pyelography was carried out and no abnormalities were seen. Urinary chromatographic studies showed elevated excretion of amino acid. Therapy with 75,000 units of vitamin D daily resulted in return of the amino acid excretion to normal and in cure of the disease as determined clinically and roentgenographically. However, the serum phosphorus level continued below the lowest level of the normal range. Attempts to correct this chemical abnormality by giving buffered sodium phosphate and citrate by mouth were unsuccessful. At the time of last report maintenance therapy consisted of 45,000 units of vitamin D daily.

CASE 3. The patient, a girl, was seen by one of the authors at four years of age after one and one-half years of unsuccessful orthopedic measures for correction of bowed legs. She had received normal doses of vitamin D since infancy. Upon x-ray study,

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Clinical and Laboratory Data in Ten Cases of Vitamin D Resistant Rickets

Case No.	Age Yr.	Age Mo.	Familial Incidence	X-ray Evidence of Rickets	Serum Calcium	Serum Phosphorus	Serum Alk. Phosphatase	Associated Anomalies	Response to Therapy with Vitamin D
1.	3	6	None	Positive	Normal	Low	Elevated	Synostosis cranei	Clinical cure
2.	2		None	Positive	Normal	Low	Elevated	None	Decided improvement
3.	4		Unknown	Positive	Normal	Low	Elevated	None	Decided improvement
4.	1	9	None	Positive	Normal	Low	Elevated	Sparse hair; congenital amputation of wrist; defective dentition	No response
5.	2	11	None	Positive	Normal	Low	Elevated	Chronic acidosis due to renal tubular defect	Untreated as yet
6.	3	9	None	Positive	Normal	Low	Elevated	None	Decided improvement
7.	3	6	3 members	Positive	Normal	Low	Elevated	None	Clinical cure; plus osteotomy
8.	1	7	3 members	Equivocal	Normal	Slightly decreased	Elevated	None	Untreated as yet
9.	3	10	3 members	Positive	Normal	Low	Elevated	None	Decided improvement
10.	2	6	3 members	Positive	Normal	Low	Elevated	None	Decided improvement

the condition of the lower extremities and wrists was observed to be typical of rickets. Blood phosphorus was 3.0 mg. per 100 cc., the alkaline phosphatase value 18 Bodansky units and the calcium content 10.0 mg. per 100 cc. Results of electrolyte studies of the blood were otherwise normal. Results of urinalysis were within normal limits. Vitamin D, 50,000 units daily, was given and the patient showed steady clinical and roentgenological improvement.

CASE 4. A 6-year-old girl, was first seen at the U.C.L.A. Pediatric Clinic with a resistant case of rickets that had been diagnosed when the patient was 21 months of age. Treatment in the past included the daily administration of up to 2,000,000 units of vitamin D. Parenteral administration of large doses of vitamin D was also attempted. According to the mother, no vitamin D had been administered during the three years preceding the child's admission to the clinic. Upon physical examination, pronounced anterior bowing of both lower legs, cranial bossing, lumbar lordosis and congenital amputation of the right forearm at the wrist were noted. Multiple ectodermal defects were present. There were several xanthomata on the legs. The hair was extremely sparse, and only four deciduous teeth remained. The child perspired very freely at normal environmental temperatures.

The amounts of electrolytes in the blood were within normal limits, with the exception of serum phosphorus, which was below the normal range. The serum alkaline phosphatase activity was 23 King-Armstrong units. Cystine crystals were not found in the bone marrow aspirate. High levels of phosphorus were repeatedly demonstrated in the urine during periods of normal and low intake of phosphorus. During the administration of calcium intravenously, the urinary content of phosphorus decreased, indicating a normal parathyroid response. During the period when no vitamin D therapy was given, rachitic bone changes, visible by x-ray examination, improved noticeably. Although most of the usual diagnostic criteria of vitamin D resistant rickets were present in this case, the possibility of hypersensitivity to vitamin D was being considered at the time of this report.

CASE 5. A 3-year-old girl was admitted to the U.C.L.A. Hospital because of roentgenographic observations and results of chemical analysis of the blood consistent with resistant rickets. Since infancy the patient had been given vitamins sufficient for normal needs. Although her appetite was poor, she ingested large amounts of orange juice. There was no familial history of rickets.

The child appeared to be alert. Moderate retardation of linear growth and lateral bowing of the lower legs were noted. The blood phosphorus was 3.8 mg. per 100 cc., calcium content 10.6 mg. per 100 cc. and alkaline phosphatase 23 King-Armstrong units. Blood electrolyte studies showed a reduced bicarbonate content on several occasions and on two occasions an elevated serum chloride content. The urine showed a reduced titrable acidity and decreased ammonia production. With rare exception, the pH of the urine remained more alkaline than pH 7.0 in spite of compensated systemic acidosis. These findings suggested that hyperchloremic renal acidosis of mild degree was the cause of the rachitic changes. In addition to increased dosage of vitamin D, oral administration of alkaline salt mixture resulted in improvement of the rickets.

CASE 6. The patient, a girl three and a half years of age, had progressive bowing of the legs since starting to walk. X-rays showed profound osteo-

malasia with other typical rachitic changes. The blood phosphorus level was 3.0 mg. per 100 cc., blood calcium 10.1 mg. per 100 cc. and alkaline phosphatase 13.9 Bodansky units. During administration of 150,000 units of vitamin D daily, toxic symptoms of nausea, vomiting and hematuria developed. Reduction of the dose to 100,000 units brought prompt relief of symptoms. Clinical response of the rickets resulted from this therapy over a period of two months. When last seen, the patient was again taking 150,000 units daily with continued improvement.

CASE 7. A 3-year-old boy, was admitted to Shriners' Hospital with complaint of bowed legs noted since he was 14 months of age. Vitamin D sufficient for normal needs had been given since infancy. In addition to typical roentgenologic features of rickets, there was a decreased blood phosphorus level (3.3 mg. per 100 cc.), elevated alkaline phosphatase (32.4 King-Armstrong units), and normal blood calcium (9.7 mg. per 100 cc.). Up to 150,000 units of vitamin D was given for six months. Bilateral femoral osteotomy was then done. Thereafter the patient was given 75,000 units of vitamin D daily and was clinically well. (The patient's mother had bilateral osteotomy for bowed legs at the age of 14 years. She had never received additional vitamin D therapy. She is now 4 feet 9 inches tall and it is assumed that she also had resistant rickets.)

CASE 8. The patient, a sister of the patient in Case 7, 2 years of age, was examined because of the familial history. No clinical symptoms of rickets were observed. X-ray films of the lower extremities, however, showed minimal rachitic changes. The blood calcium was 10.3 mg. per 100 cc., phosphorus 3.7 mg. per 100 cc. and alkaline phosphatase 24.0 King-Armstrong units.

CASE 9. A 4-year-old girl had a history of increased lateral bowing of the legs, observed over a period of a year. Her mother had had rickets and, at the age of six years, had had bilateral osteotomy for repair of the bowing. The mother was 4 feet 7½ inches tall. Less than normal linear growth and advanced rachitic changes were observed in roentgen studies. The phosphorus content of the blood was 3.7 mg. per 100 cc., calcium 10.4 mg. per 100 cc. and alkaline phosphatase 26 King-Armstrong units. After six weeks of therapy with 100,000 units of vitamin D daily, improvement was observed roentgenographically.

CASE 10. When the sister of the patient in Case 9, 28 months of age, was examined, diminished stature was the only abnormality noted clinically. X-ray films of the long bones showed definite rachitic changes. Blood alkaline phosphatase was 45.0 King-Armstrong units, phosphorus content 3.2 mg. per 100 cc. and calcium content 9.6 mg. per 100 cc. Rachitic changes in the bones, as roentgenographically observed, were improved after six weeks of vitamin D therapy.

DISCUSSION

The usual clinical manifestations of vitamin D resistant rickets are similar to those of vitamin D deficiency rickets. Both probably begin within the first year, but whereas the latter usually is diagnosed early, rarely is resistant rickets diagnosed in a patient less than one year of age, perhaps because suspicion of rickets is not high in a patient so young who is receiving the usual daily supplement of vitamin D. Usually with both kinds of rickets the first symptom noted is bowing of the legs with concomitant shortening of stature. The bowing may be in a lateral, medial or anterior direction, lateral most often. Cranial bossing, beading of the ribs and enlargement of the knees, wrists and ankles may also be present.

In the very early stages of the disease, rickets cannot be detected roentgenographically. This is particularly true if the roentgen studies do not include the distal parts of the lower extremities at the time of evaluation of bowed legs, since the earliest changes occur at the site where the bone growth is most rapid. The first roentgenographically observable changes occur at the epiphyseal plate. Normally the plate is sharply defined, but in a patient with rickets there is a frayed appearance at the metaphyseal-epiphyseal junction which is caused by irregular osteoblastic deposition of bone salt resulting from continued, but disorderly, resorption of the cartilagenous osteoid tissue in this rapidly growing area. The most common sites of such involvement in rickets are the distal femur and the distal ends of the ulna and tibia. As the rachitic process continues, demineralization of the shaft occurs, owing to a loss of lime. As a consequence of this softening of the bone, bowing and, occasionally, fractures may occur.

Chemical studies of the blood in a typical case show decreased serum phosphorus concentration and elevated alkaline phosphatase activity. Blood calcium levels may be normal or slightly depressed.

Resistant rickets is generally considered to have a familial basis, although reports of sporadic cases are numerous.

Pathogenesis

Fanconi's concept of "phosphate diabetes" due to selective tubular deficiency as the primary mechanism in resistant rickets is in general agreement with that of most investigators. Robertson and co-workers[20] were the first to express this concept. Other observers, including Winberg and co-workers[25] who recently reported on the subject, could not demonstrate the increased tubular excretion of phosphorus in untreated resistant rickets. Perhaps certain cases may have a different pathogenesis, and perhaps not all vitamin D resistant rickets is of the same type.

However, most of the cases described herein, as well as the majority of cases reported in the literature, appear to be a variant of the Debre-de Toni-Fanconi syndrome, where some degree of tubular dysfunction is evident. In two of the cases reported herein, abnormal urinary amino acid excretion was demonstrated by paper chromatographic methods. Fishman and Jonxis also observed this condition in patients with vitamin D resistant rickets.[10,15,16] The amino-aciduria may possibly result from the same basic defect as does the phosphaturia.

Although faulty intestinal absorption of vitamin D may bring about the clinical features of rickets, this defect was not present in the patients under consideration. Normal vitamin D levels may be demonstrated in the blood of patients with vitamin D resistant rickets at a time when the patient is receiving only small doses of vitamin D by mouth, even while the disease is in its active state.[3,8]

There are two primary sites of action of vitamin D. The greatest action is in the intestine, where vitamin D increases the absorption of ingested calcium and, as a consequence, the absorption of ingested phosphorus. Vitamin D also acts on renal tubules. Its mechanism of action there is not well understood. Albright postulated that the greater tubular efficiency of phosphate reabsorption is the result of parathyroid inhibition which has resulted from the high intestinal absorption of calcium. In patients with vitamin D resistant rickets, this mechanism is further complicated. The reasons for the hyperphosphaturia and amino-aciduria are not as yet fully explained. Jonxis was unable to demonstrate abnormal amino-aciduria in patients with hyperparathyroidism, implying that parathyroid hormone is not responsible for amino-aciduria in resistant rickets.[14] Thus, even though patients with vitamin D resistant rickets are known to have increased parathyroid activity, it would appear that this is a secondary rather than a primary phenomenon. Compensatory parathyroid hyperactivity accounts only for the normal blood calcium levels usually found in this condition. From the available evidence, it would seem that the primary defect in vitamin D resistant rickets lies within the renal tubular cell and is associated with a poorly understood enzymatic process which may be dependent upon vitamin D for its action.

Differential Diagnosis

Vitamin D resistant rickets must be differentiated from conditions which may cause similar abnormality in growth of bones. Congenital abnormalities of the lower extremities, such as femoral bowing, coxa varum, coxa valgum and bony defects associated with dimpling of the overlying skin, must be considered. Other, more generalized congenital defects, such as chondrodystrophy and osteochondrodystrophy, may simulate vitamin D resistant rickets in the early forms of each. These other conditions are not associated with abnormalities in the blood concentrations of calcium, phosphorus and alkaline phosphatase, nor do they respond to therapy with vitamin D.

Rathbun[21] recently described an inborn error of metabolism which is associated with an abnormality in the metabolism of alkaline phosphatase.[21] This condition may simulate vitamin D resistant rickets in clinical and radiological characteristics. Differential diagnosis from resistant rickets is made on the basis of chemical studies of the blood. In this condition, which has been called "hypophosphatasia," the blood calcium levels are normal or high, the serum phosphorus levels are normal, and the alkaline phosphatase activity of the serum is depressed or absent. Vitamin D in large doses does not improve the condition.

Lead poisoning in its chronic form has, at times, been associated with amino-aciduria, hypophosphatemia and rachitic changes in the bones.[6] The chemical contents of the blood may also be abnormal. These rachitic changes are the result of an excessive loss of calcium in the stool as calcium soaps. In addition, there is a failure of intestinal absorption of the fat-soluble vitamin D. Steatorrhea, therefore, may result in rickets which does not respond to oily solutions of vitamin D administered orally.

When it has been established that the problem is truly that of rickets which does not respond to the usual low dosage level which will cure vitamin D deficiency rickets, one must consider whether additional metabolic defects are present. Renal acidosis, as seen in the classical Fanconi syndrome, and the hyperchloremic syndrome described by Albright must be considered. Therapy with large doses of vitamin D alone in these conditions is not sufficient.

Treatment

Satisfactory clinical healing of the rachitic lesions in patients with uncomplicated vitamin D resistant rickets usually results when from 50,000 to 150,000 units of vitamin D is given daily. Occasionally a patient will require considerably larger doses before a response can be noted. The vitamin D should be administered by mouth, since there is no defect in the absorption by this route.

The earliest response to proper treatment can be best evaluated by x-ray films of the bones. This is manifest by finding a linear increase in density in the rachitic metaphysis at the rapidly growing ends of the long bones, which results from an increased and more orderly deposition of bone salt in this area and eventually progresses to a broad, dense, transverse line. As healing continues, x-ray films

will show a disappearance of the cupping, as well as a decreased distance between the calcified portions of the metaphyses and epiphyses. Later, the density of the shafts of the long bones increases. Gradual disappearance of the bowing and other bony deformities accompanies this process. Whether the deformity will be completely overcome depends upon the severity of involvement at the beginning of therapy, the age at which therapy is begun, and the adequacy of therapy on an individual basis.

In addition to radiological observation of progress, chemical evidence may be obtained of the effect of large doses of vitamin D. The earliest of these is a return of the elevated alkaline phosphatase activity of the serum to normal levels. This evidence may not be present as early as radiologic evidence of healing. In resistant rickets, unlike ordinary rickets, the return of the serum phosphorus level to normal occurs late. In some patients this may not occur until several years after therapy is begun.[11,22] (Attempts to accelerate the return of inorganic phosphorus level to normal in one of the patients treated by the authors, by increasing the dietary intake of phosphorus, were unsuccessful.)

Theoretically, the administration of citric acid and citrate should be of some benefit. This organic acid combines with bone salt as an integral part of the crystalline framework of bones. The citric acid content of bone may be experimentally increased by the administration of vitamin D. The citric acid content of the blood rises during the administration of vitamin D, as well as with calcium administration alone. Increasing the amount of phosphorus in the diet appears to have no effect on blood citric acid levels.[5] Harrison[12] demonstrated that the level of citric acid in the blood in children with vitamin D deficiency rickets averages only 1.5 mg. per 100 cc., as compared with the normal of 2.5 mg. The administration of vitamin D caused this level to return to normal. In rats, diets low in calcium and phosphorus will produce rickets and the administration of citric acid and sodium citrate will promote healing of rachitic lesions, even though the rat continues to receive a diet low in calcium and phosphorus.[26]

In spite of these fragments of indirect evidence which would suggest that additional citrate should be of benefit in the therapeutic regimen of patients with vitamin D resistant rickets, this has not been the case.[8] In another attempt to accelerate the return of the serum inorganic phosphorus level to normal in one of our patients, we administered large doses of citrate in addition to vitamin D. There was no detectable improvement in the serum phosphorus level.

The dangers of using large doses of vitamin D can be great, unless proper precautions are taken. Hypercalcemia with resultant soft tissue calcification and particularly renal calcification may result unless adequate control is maintained. We have arbitrarily chosen 12 mg. of calcium per 100 cc. of blood as the upper safe limit. When this level is reached, regardless of the state of healing of the rachitic process, the dosage of vitamin D must be reduced. The content of calcium in the blood of all patients receiving large daily doses of vitamin D is determined monthly. Although we have attempted to evaluate the calcium levels of these patients by use of the Sulkowitch reagent for testing the urine, this has not proved satisfactory. The correlation of results of this urine test with blood calcium determinations has been poor; in some cases hypercalcemia has developed in the face of normal results of the urine tests.

Although the dosage necessary for promoting healing early in the disease may be somewhat greater than the dosage required after healing is well under way, there appears to be no predictable formula for calculating individual dosage levels. In our experience, repeated evaluation over periods as long as a year may be required to reach the proper dosage level, since hypercalcemia may develop very slowly. A complicating situation results when a patient receiving large doses of vitamin D is suddenly immobilized. In such circumstances the blood calcium level may rise to dangerously high levels, with resultant deposition of calcium in soft tissues, particularly in renal tubules. It seems desirable to discontinue high levels of vitamin D well in advance of predictable periods of immobilization, such as for elective operation to correct orthopedic deformities. Nausea and vomiting may be due either to the toxic effects of overdosage or to the gastric irritation of the vitamin D per se.

The continuing high requirement of vitamin D is usually evident until the end of the growth period, when the epiphyses close. In the majority of children treated before the age of five years, surgical correction of the deformities is unnecessary. Surgical results are poor in patients who have had no previous vitamin D therapy, and a return of the deformities is to be expected.

Associated Abnormalities

Three of the ten children included in this report had associated congenital abnormalities. The patient in Case 1 had premature closure of the cranial sutures with resultant increased intracranial pressure. Although this anomaly is not uncommon with other forms of congenital disorders of bone metabolism, it has been reported only twice previously in association with vitamin D resistant rickets.[7,13] In Case 5 the patient had chronic acidosis associated with alkaline pH of the urine and decreased ability of the renal tubule to produce ammonia. In this

case the bone disease did not respond to vitamin D until alkali therapy was added. The patient in Case 4 had multiple ectodermal defects in addition to the apparent resistance to extremely high doses of vitamin D. A similar association of vitamin D resistant rickets and ectodermal defects was reported by Imerslund.[13] In the case here reported, radiologic improvement of the rachitic deformities occurred during a three-year period when no vitamin D was given. Spontaneous improvement of the rachitic process is very unusual in these patients. Hence it is possible that the patient in Case 4 may be hypersensitive to vitamin D rather than resistant to it. A similar case was reported by Van Creveld.[23]

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Diabetic Patients with Myocardial Infarction

The Diagnostic Accuracy of the Electrocardiogram

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• **In a study involving interpretation of electrocardiograms of two groups of patients who had myocardial infarction—one a group of diabetic patients and the other group made up of nondiabetic—the electrocardiogram was found to be considerably less accurate in the diagnosis of myocardial infarction in the diabetic patient than in the nondiabetic subject. This is due to the fact that the patterns which mask the diagnosis of myocardial infarction in nondiabetic patients occur more frequently in diabetic individuals. It is important to note that in no instance were the electrocardiograms interpreted as normal in the diabetic group.**

THE ACCURACY of the electrocardiogram has been well established in the diagnosis of myocardial infarction in nondiabetic persons.[3] The assumption has been that the electrocardiogram should be just as able to corroborate the diagnosis of myocardial infarction in diabetic patients. Joslin[1] stated, "In diabetic patients the common electrocardiographic evidences of coronary occlusion are occasionally not obtained or [are] obscured for various reasons." In a survey of the American literature no studies substantiating this impression were found.

It has been often noted at the electrocardiographic clinicopathological conferences conducted at the Los Angeles County General Hospital that when the electrocardiogram failed to reveal the presence of a proved myocardial infarction, the patient usually had diabetes mellitus. The present study was undertaken to determine if any disparity exists in the accuracy of electrocardiographic diagnosis of myocardial infarction between diabetic and nondiabetic persons.

METHODS

The cases for study were obtained from the autopsy files of the Los Angeles County General Hospital for the years 1948 to 1952 inclusive. In the first two years of the study, electrocardiograms consisted of the six chest leads (CF) in addition to the limb leads. In the second two years the augmented unipolar and V leads supplanted the CF leads.

Data on two groups of patients with "autopsy proved" myocardial infarctions were compared. The first group consisted of diabetic patients who had myocardial infarction, observed at autopsy, and whose records included electrocardiograms with precordial leads. The second series included 52 consecutive nondiabetic persons who had electrocardiograms and in whom myocardial infarction was observed at autopsy. Each series consisted only of cases in which it could be definitely determined that the infarction had occurred prior to the taking of the electrocardiograms. In two sets of readings for the diabetic group 53 and 56 cases met this criterion. The usual accepted electrocardiographic criteria were used in diagnosing the presence of a myocardial infarction. In addition if the electrocardiograms were interpreted as showing acute anoxia, injury or ischemia patterns, these were also counted as diagnostic of infarction. In these cases the assumption was that the actual muscle death had occurred shortly after the electrocardiogram was taken. In all cases the infarcts were transmural.

Two sets of interpretations of all the electrocardiograms were used. The first consisted of the interpretation by members of the electrocardiographic department, which is composed of junior and senior attending physicians of the medical staff of the Los Angeles County General Hospital, as well as a few third year medical residents. The second set was read by a consulting cardiologist of the senior attending staff of the Los Angeles County General Hospital.* The following information was available to all the readers: Age, sex, blood pressure, and whether or not quinidine or digitalis was being administered. Only the first set of readers was aware of the clinical impression. The age of the infarct was determined from the information available in the autopsy protocols on the basis of the gross and microscopic descriptions of the pathologic material according to the criteria set forth by Mallory and co-workers.[2] As the age of the infarct in the first three weeks after it occurs can be judged fairly accurately from the histologic features, the material for this study was divided into two groups. The infarcts in which the pathological changes were such that they could be classified as occurring within

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TABLE 1.—*Accuracy of Diagnosis of Infarction on Basis of Electrocardiograms in Diabetic and Nondiabetic Patients*

Reader	Diabetic			Nondiabetic		
	Number Correct	Number Incorrect	Total	Number Correct	Number Incorrect	Total
Cardiologist	37 (66%)	19 (34%)	56	46 (88%)	6 (12%)	52
Staff	27 (51%)	26 (49%)	53	42 (81%)	10 (19%)	52

TABLE 2.—*Accuracy of Diagnosis of Acute Infarction on Basis of Electrocardiograms in Diabetic and Nondiabetic Patients*

Reader	Diabetic			Nondiabetic		
	Number Correct	Number Incorrect	Total	Number Correct	Number Incorrect	Total
Cardiologist	31 (72%)	12 (28%)	43	39 (93%)	3 (7%)	42
Staff	21 (50%)	21 (50%)	42	35 (83%)	7 (17%)	42

three weeks of the time that the electrocardiograms were recorded were designated as recent infarcts. The remaining ones were classified as old infarcts. In all instances the area of infarction or scar tissue measured two centimeters or more in diameter.

RESULTS

The correctness of the electrocardiographic diagnosis of myocardial infarction as proved at autopsy in the diabetic and the nondiabetic groups is shown in Table 1. Both groups included all infarcts regardless of age. When results in the nondiabetic group were compared with those in the diabetic group, the inaccuracy of the electrocardiogram became apparent. In 52 nondiabetic patients myocardial infarction was correctly diagnosed by the staff in 42 or 81 per cent of the cases and by the consulting cardiologist in 46 or 88 per cent of the cases. These results compare favorably with those of Zinn and Cosby[3] who reported 80 per cent accuracy in a similar series of nondiabetic patients. In diabetic patients myocardial infarction was correctly diagnosed by the staff in only 27 of 53 cases, or 51 per cent, and by the consulting cardiologist in 37 of 56 cases or 66 per cent. These results were analyzed statistically and proved to be at a significant probability level.† The slight difference in accuracy between the two sets of readers did not prove to be significant.

It was thought that the inclusion of both recent and old infarcts in the same group was affecting the conclusions. Therefore the data were recalculated including only infarcts of three weeks or less in duration (Table 2).

The accuracy of the staff was 21 out of 42 cases or 50 per cent in the diabetic patients and 35 out of 42 or 83 per cent in the nondiabetic patients. The accuracy of the consulting cardiologist was 31 out of 43 or 72 per cent in the diabetic group and 39 out of 42 or 93 per cent in the nondiabetic group.

†All statistical analyses were determined by either the method of chi squared (x^2) or the Fisher exact method for fourfold tables. The probability that these results could have occurred by chance was one in one thousand times.

TABLE 3.—*Effect of Location of Infarction on Accuracy of Diagnosis by Electrocardiogram*

Location of Infarct	Number Correct	Number Incorrect	Total
Involving septum	26	11	37
Anterior septal	16	6	
Posterior septal	9	3	
Anterior posterior septal	0	2	
Pure septal	1	0	
Not involving septum	10	7	17
Anterior	4	1	
Posterior	6	6	

TABLE 4.—*Electrocardiogram Patterns Obscuring Diagnosis (Readings by Consulting Cardiologist)*

	Number of Cases
Left ventricular hypertrophy	6
Left bundle branch block	2
Right ventricular hypertrophy	1
Right bundle branch block	2
Supraventricular tachycardia	1
Auricular fibrillation	1
Digitalis effect	3
Hypopotassemia*	2
Abnormal electrocardiogram	1

*Actually potassium levels were not abnormal.

The difference in accuracy as between the two groups was still significant.

An attempt was made to analyze the factors in the diabetic patients that may have accounted for these differences. When the groups were subdivided for this purpose, they became rather small and definite conclusions were not warranted. The diagnosis of infarction was made with equal facility whether the area of infarction involved the anterior, posterior or septal walls (Table 3).

The effects of electrolyte imbalance on electrocardiograms are well known. In this series most of the patients had a normal carbon dioxide combining power and nonprotein nitrogen blood levels at the time the electrocardiogram was recorded. In the few instances in which serum potassium levels were de-

termined, they were normal. Acidosis was present in a total of ten cases. In eight of these ten cases the presence of an infarct was indicated by the electrocardiogram.

Neither the age nor sex of the patient, nor the duration and severity of diabetes had any bearing on the electrocardiographic accuracy.

Left ventricular hypertrophy, digitalis effect and bundle branch block accounted for the majority of interfering patterns (Table 4).

These patterns were similar to those listed by Zinn and Cosby[3] as interfering with the diagnosis of myocardial infarction in nondiabetic patients. It should be noted that in the presence of a known myocardial infarction, none of the electrocardiograms of the diabetic individuals was read as normal.

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Spontaneous Splenic Rupture in Mononucleosis

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• **Infectious mononucleosis is a disease entity with many and various manifestations. Suspicion of the disease is of the utmost importance. When indicated, adequate tests often repeated must be made to prove or disprove a suspicion of infectious mononucleosis. The disease is usually a benign condition; one of the more serious complications is "spontaneous" splenic rupture. Whether rupture is indeed spontaneous or is caused by relatively light trauma to a weakened organ is debatable. Splenectomy is the treatment for this complication; it does not cure the underlying disease. Once the diagnosis of infectious mononucleosis has been established, abdominal examinations should be limited and cautious.**

INFECTIOUS MONONUCLEOSIS has been described as a protean disease which involves the reticuloendothelial system. It may affect the entire body with equal intensity or be manifest in symptoms relating to one or a few structures of this system. The onset is usually associated with malaise, upper respiratory tract infection, weakness, low grade fever, mild pharyngitis and enlargement of lymph nodes. Chemotherapy helps little and there is a lingering illness of longer than is normally expected. Approximately seven to ten days after onset, the heterophil antibody reaction becomes positive in significant diagnostic dilutions. If the disease is suspected yet not immediately proved by laboratory aids, tests for it should be repeated at regular intervals. It is important to suspect the disease when the lymph nodes are enlarged, for correct diagnosis greatly decreases the mortality. In the majority of cases, if properly treated with rest and symptomatic medication, it is an innocuous and benign condition. Once therapy is begun, the patient has symptomatic improvement and is likely to insist on resuming normal activities. The physician must not be influenced by the wishes of the patient. In certain instances the disease may be fulminating and fatal.

Spontaneous splenic rupture is one of the rarer complications. It occurred in two patients who were treated at Norton Air Force Base Hospital, San Bernardino, California. One of the patients was observed by the authors (Case 2). The report of Case 1 was abstracted from hospital records.

CASE 1. A 31-year-old male officer was admitted to the hospital on April 2, 1954. Ten days before admission the patient noticed the onset of nocturnal chills, fever and myalgia; and two days before admission, generalized lymph node enlargement and pronounced malaise developed.

Upon examination the patient was observed to be well developed and well nourished, in no acute distress, well oriented and cooperative. The blood pressure was 138/74 mm. of mercury, the pulse rate 88, the temperature 98.6°F. Diffuse pharyngitis, pronounced enlargement of cervical lymph nodes and moderate axillary lymph node enlargement were noted. No abnormalities were noted in the heart and lungs. The liver, palpable one and a half fingerbreadths below the right costal margin, was firm and slightly tender. The splenic edge was barely palpable.

Submitted June 7, 1956.

Results of urinalysis were within normal limits. Leukocytes numbered 18,200 per cu. mm. of blood —17 per cent neutrophils, 30 per cent lymphocytes, and 53 per cent abnormal lymphocytes. Erythrocytes numbered 4.2 million per cu. mm. and the hematocrit was 36 per cent. The sedimentation rate was 26 mm. in one hour. Heterophil reaction was positive in 1 to 1,792 dilution.

The patient was kept in bed and was given symptomatic treatment. He became quite nauseated on the morning of April 4 and had several bouts of vomiting. Several hours later the patient began to complain of intermittent pains in the left upper quadrant of the abdomen, which became progressively worse during the night.

On April 5 the abdomen was moderately distended with shifting areas of dullness to percussion in the flanks and positive fluid waves. Leukocytes numbered 16,050 per cu. mm.—29 per cent neutrophils and 40 per cent lymphocytes (30 per cent reported as abnormal). Erythrocytes numbered 2.6 million per cu. mm. and hemoglobin content was 9.5 gm. per 100 cc. The hematocrit was 26 per cent. A diagnosis of "acute surgical abdomen" was made. The abdomen was opened and the spleen was found to be enlarged and ruptured. It had become partially walled off by the stomach, colon and omentum. The spleen was removed.

The pathological report stated that the gross specimen consisted of a spleen 15 x 10 x 6 cm., weighing 432 gm. The capsule was almost completely fallen away, leaving the underlying pulp naked. On section, the specimen was found to be extremely pulpy with a loss of the usual architectural features.

Upon microscopic examination the sinusoids were observed to be filled with cells. Normal and atypical lymphocytes were seen. There were numerous areas where the spleen showed microscopic cleavage

planes and these areas were also filled with a similar cell in a protean coagulation. The pathological diagnosis was infectious mononucleosis of the spleen with rupture.

The patient made an uneventful postoperative recovery and was discharged on April 26, 1954. He was readmitted on June 7, 1954, with complaint of increasing fatigue, bloating and anorexia. Seven days previously a low grade fever had developed. At the time of admission the sclerae were decidedly jaundiced. A diagnosis of homologous serum hepatitis secondary to blood transfusion was made. Conservative treatment was given and the patient recovered. Thereafter he remained asymptomatic. The interval between the blood transfusion and the onset of symptoms on the second admission was 50 days—a relatively short incubation period for homologous serum hepatitis. The second illness may have been a relapse of infectious mononucleosis. Clinical hepatitis with jaundice is not an infrequent complication of infectious mononucleosis, as the liver is richly endowed with Kupffer cells, a part of the reticuloendothelial system.[3]

CASE 2. A 23-year-old white male airman was admitted to the hospital on December 11, 1954. A month previously the patient had had a mild upper respiratory tract infection that lasted four or five days. Three weeks later, a week before admittance, while engaged in a moderately strenuous training program, he had fallen several times, striking his abdomen against a pack that he carried. Four days before admission a nonproductive cough associated with weakness and extreme malaise developed. While taking a shower an hour before hospitalization, the patient had sudden, severe pain in the left upper quadrant of the abdomen. The pain was accentuated by coughing and deep inspiration.

Upon examination the patient was observed to be well developed and well nourished, well oriented and cooperative. The blood pressure was 126/70 mm. of mercury, the pulse rate 104, respirations 20 per minute and the temperature 100.2°F. The skin was pale, with cold, clammy perspiration. The posterior pharyngeal wall was of a dull red hue. No enlargement of lymph nodes was noted in the cervical or axillary regions. The heart and lungs were normal. Moderate voluntary splinting of the muscles of the upper abdomen was noted. No masses were palpated. The outline of the spleen could not be felt.

Leukocytes numbered 10,830 per cu. mm.—neutrophils 40 per cent, lymphocytes 46 per cent, abnormal lymphocytes 13 per cent, basophils 1 per cent. Erythrocytes numbered 4.3 million per cu. mm. and the hemoglobin content was 13.8 gm. per 100 cc. Results of urinalysis were within normal limits. The heterophil titer was positive in 1 to 3,584 dilution. Guinea pig absorption tests were specific for infectious mononucleosis during this time.

A diagnosis of infectious mononucleosis with possible "spontaneous" splenic rupture was considered. No abnormalities were noted in x-ray films of the abdomen and chest taken at the time of admission.

Six hours after admission, the patient complained of increasingly severe pain in the left upper quadrant of the abdomen. The patient was observed closely and repeatedly examined. The blood pressure and pulse remained stable. Left upper abdominal pain continued but it was intermittent and decreasing in severity. Blood examinations were done repeatedly and the hematocrit and hemoglobin content slowly decreased. In a plain film of the abdomen taken 24 hours after admission, mild gastric dilatation and the presence of a mass displacing the stomach in the left upper quadrant were observed. The patient was given a transfusion of 500 cc. of whole blood and pronounced symptomatic improvement occurred immediately.

On December 14, 1954 the patient complained of a sudden severe pain in the left upper quadrant of the abdomen, associated with pain in both shoulders. He was nauseated and became cold and clammy. The blood pressure was 90/60 mm. of mercury and the pulse rate 130. Transfusion of whole blood was started and the patient was taken to surgery. At operation a large walled-off mass was found in the left upper quadrant of the abdomen. In the left subdiaphragmatic space there were multiple old clots and a pulpy splenic mass which was bleeding from multiple rents. The splenic capsule was almost completely avulsed.

The pathological report said that the specimen consisted of a spleen weighing 310 gm. and measuring 15 x 13 x 5.5 cm. The external surface was pale brown. The gastric surface of the spleen was interrupted by numerous large, irregular gaping rents extending the entire length of the spleen. There were numerous dark red blood clots that measured up to 10 cm. in greatest dimension. Upon microscopic examination it was observed that the usual architectural pattern was greatly distorted by diffuse hyperplasia of the reticuloendothelial elements. The usual germinal centers were reduced in number and size. Within the sinusoids there was a typical cell that is seen in infectious mononucleosis—a large oval cell with pale cytoplasm and oval vesicular nuclei in which the chromatin is rather prominently clumped. Also within the sinusoids there were numerous polymorphonuclear cells, eosinophils, macrophages and a number of metamyelocytes. The diagnosis was infectious mononucleosis with splenic involvement and recent rupture of the spleen.

Postoperative recovery was uneventful. After ten days he was placed at complete bed rest for a period of one month as treatment of infectious mononucleosis. Two weeks following the operation heterophil reaction was positive in 1 to 890 dilution. Six weeks later positive reaction occurred at 1 to 224 dilution. Results of liver function tests were within normal limits. The patient was then completely asymptomatic. Heterophil reaction and liver function tests were done at monthly intervals for a period of six months with the thought that if nausea,

vomiting, anorexia or malaise developed again and were associated with a rise in the heterophil titer, the patient would be returned to bed rest.

COMMENT

The mortality rate associated with spontaneous splenic rupture in infectious mononucleosis is extremely high. In 23 cases reported, there have been five deaths or a mortality rate of 22 per cent. Even more impressive was the 40 per cent mortality rate in cases in which infectious mononucleosis was not diagnosed preoperatively or before death.[5] A preoperative diagnosis of infectious mononucleosis is of prime importance in decreasing the mortality rate. Since 1932, when Paul and Bunnell[4] discovered the presence of agglutinins and hemolysins for sheep erythrocytes in the serum of patients with infectious mononucleosis, the diagnosis of this disease has been on a firmer foundation.

Once the diagnosis has been established, the ever present possibility of splenic rupture must be borne in mind. The question as to whether the spleen actually ruptures spontaneously has been raised many times. There is extensive loss of normal splenic architecture in infectious mononucleosis. In the capsule and trabeculae considerable cellular infiltration occurs, with edema and so-called cloudy swelling. The basic structure of the spleen is greatly weakened. There is no doubt that the diseased organ is much less likely to withstand trauma than is a normal spleen.[5]

In Case 2 there was definite history of repeated concussive trauma. In Case 1 the diagnosis of infectious mononucleosis was made immediately, but even so it is probable the abdomen was palpated many times in the course of examination. In cases in which definite diagnosis is not made promptly, the patient undergoes many abdominal examinations for diagnosis. Frequently in reported cases, the onset of severe abdominal pain was related to trauma and stress such as that associated with vomiting and straining during bowel movement.[2] It would seem possible that even minor trauma of this kind might have relatively great effect on a severely diseased spleen. Once the diagnosis of infectious mononucleosis has been made, examination of the abdomen should be minimal, cautious and gentle.

Smith and Custer[5] noted that rupture of the spleen takes place at least three weeks after onset of the infectious mononucleosis. Presumably it is during this period that the capsular and trabecular changes progress to the point of rupture either "spontaneously" or through slight trauma. The symptoms of onset of "spontaneous" rupture of the spleen in infectious mononucleosis are quite variable. Rupture may be associated with onset of severe pain in the left upper quadrant of the abdomen, which may or may not be constant and accompanied by signs of intense shock. Gastric dilatation and displacement of the stomach by a soft tissue mass from the left upper quadrant as seen on a plain film are highly suggestive evidence. It is important to repeat the hemoglobin and hematocrit determinations for signs of slow bleeding which may not be clinically evident. It has been noted by various observers that splenic rupture was followed by reversal of the cell differential usual in infectious mononucleosis, with leukocytes and neutrophils rather than lymphocytes becoming predominant.[6] This was not noted in the two cases herein reported. A further aid in diagnosis is paracentesis. If blood is obtained, the diagnosis is supported; but even if it is not, the suspicion of ruptured spleen cannot be allayed, for the organ may be walled off. Once the diagnosis is made, operation should be done immediately.[1]

Splenic rupture with hemorrhage progresses in two ways. One is by immediate hemorrhage with exsanguination and death. This may occur within three hours after the onset of acute symptoms of abdominal pain. The other way is by delayed hemorrhage—the delay being caused by tamponade, as happened in both the cases reported herein. In each, at the time of operation, it was noted that a partial walling-off had taken place. Tamponade occurs in the following manners: Simple rupture with clot formation, simple or multiple ruptures with omental plug, simple or multiple ruptures with walling-off by the stomach, colon and omentum.[7]

It is impossible to estimate the incidence of infectious mononucleosis and the complication of splenic rupture. It is probable that it is rather rare.[3] In the differential diagnosis of acute abdominal pain it must always be considered. This condition may simulate such entities as a ruptured peptic ulcer, acute cholecystitis, acute hemorrhagic pancreatitis, acute appendicitis with peritonitis, acute mesenteric thrombosis and acute intestinal obstruction.

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Urinary Diversion in Therapy of Pelvic Cancer

An Appraisal of Ileal-Ureteral Anastomosis

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• **In 43 cases, diversion of the urinary stream was carried out by means of an end-to-side anastomosis of ureters into an ileal segment. Forty-one of these operative procedures were performed in conjunction with the primary or secondary surgical treatment of malignant neoplasm arising in the pelvis.**

There were six postoperative deaths in this group of patients, none due to the urinary diversion.

The remaining patients were observed for periods of from three to sixty months, the mean average eighteen months. During that period, only one patient died (at 42 months) as the result of urinary diversion. In that case death came about because the patient insisted on wearing a Foley retention catheter rather than an ileostomy bag, and the catheter perforated the ileal segment.

In only three of the patients did pyelonephritis develop, and the disease was controlled by giving chemotherapeutic agents. In ten patients, some changes in postoperative intravenous pyelograms were observed.

WITH THE DEVELOPMENT of operative treatment of cancer in the pelvis to a point where it appeared it might be used for permanent control of the disease, it became obvious that urinary diversion operations of most types were unsatisfactory as far as the life expectancy of a patient was concerned. With most of these diversions—cutaneous ureterostomy or anastomosis of the ureters into the intact bowel—there was a high proportion of recurrent ascending renal infection and, consequently, progressive renal damage. It was this damage, rather than the disease for which they were treated, that limited the patients' life expectancy.

Surgeons began seeking urinary diversion of a kind that could provide the patient with a minimum risk to life from recurrent infection, freedom from hyperchloremic acidosis (reabsorption of electrolytes) and an acceptable substitute for the urinary bladder from the esthetic point of view. Under ordinary circumstances, colostomy of itself represents no problem to the average patient. Patients are trained to bowel movement once a day by means of an irrigation and then go about without the burden of a colostomy bag or appliance other than a flat of gauze placed over the artificial anus. When it becomes necessary to utilize the intact bowel with a colostomy for the excretion of urine, an esthetic problem is automatically created.

Bricker[1] resolved this problem when he employed an isolated ileal loop for the diversion of the urinary stream, utilizing Cordonnier's[4] method of ureterointestinal anastomosis. Bricker isolates a segment of ileum 8 to 12 inches in length from the intestinal tract. The continuity of the intestine is reestablished by means of an end-to-end ileo-ileostomy, utilizing two layers of interrupted silk sutures for the anastomosis. This provides an isolated segment of intestine with an intact supply of blood. The proximal end of this segment is closed, usually in two layers, by means of interrupted black silk sutures; and the ureters are anastomosed to this isolated segment at the level of sacral promontory (Figure 1). For these anastomoses 5-0 chromic catgut is used in an interrupted fashion to produce an end-to-side, mucosa-to-mucosa anastomosis of the ureter to the ileal segment. It takes four to six such sutures to produce a satisfactory approximation of ureter to bowel. This junction is reinforced by two to four basting sutures of fine black silk which comprise a "second" layer for the anastomosis. The distal end of ileum is then brought out through a stab wound in the right lower quadrant of the abdomen. This is done after a stab wound has been prepared and a piece of skin approximately 2.5 cm. square is excised from the skin about the stab wound. The edges of ileum, which are withdrawn through the stab wound, are then sutured to the skin by means of interrupted fine black silk sutures. No attempt is made to close the defect in the lumbar gutter of the right lower quadrant of the abdomen. At the close of the operative procedure, a latex bag is cemented over the ileostomy opening to collect the urine.

On theoretical grounds, this type of urinary diversion seems best because it provides a ureteral anastomosis that is less liable to stricture and a single aqueduct that makes the collection of the excreted urine a relatively simple affair. This diversion provides a lessened likelihood of stricture at the ureteroileal anastomosis and an unobstructed flow of urine,

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TABLE 1.—*Total Case Material*

Female genital		18
Cervix	12	
Corpus	3	
Other	3	
Bladder		16
Colon		7
Rectum	6	
Sigmoid	1	
Radionecrosis and fistula		2
Total		43

TABLE 2.—*Kinds of Operations in 43 Cases in Which Ureteral-Ileal Anastomosis Was Carried Out*

Kind of Operation	Number	Postoperative Death	Operative Mortality (Per Cent)
Total exenteration	23	5	21.7
Anterior exenteration	4	0	....
Total cystectomy	14	1	7.1
Urinary diversion	2	0	....
Total	43	6	14.0

which is collected in the bag. With no obstruction to the continued flow of urine, the incidence of recurrent ascending renal infection is reduced. Also the entire urinary diversion is free of the intact gastrointestinal tract and, therefore, there is no contamination by the fecal stream.

The purpose of the present communication is to review the author's experience with this type of urinary diversion in the treatment of patients with pelvic cancer and allied problems. The case material has been drawn from several sources* and covers a period of time from 1949 to 1955. A few of the earlier cases in this series from the Ellis Fischel State Cancer Hospital were included in a review of 106 such urinary diversions that were reported by Bricker.[2]

In all, there were 43 cases in which ileal segments were employed to divert the urinary stream (Table 1). Forty-one of these operations were carried out in conjunction with the primary or secondary surgical treatment of neoplasms arising in the pelvis. The remaining two cases were instances in which urinary fistulae had developed following heavy irradiation to the pelvis in the treatment of cancer of the cervix. The operations that were employed ranged from total pelvic exenteration in the treatment of pelvic cancer to simple urinary diversion in the cases of radionecrosis and urinary fistulae (Table 2). In the entire series, there were six postoperative deaths, none of them attributable to the urinary diversion.

*The Veterans Administration Hospital, Jefferson Barracks, Mo., The Veterans Administration Hospital, Aspinwall, Pa., The Ellis Fischel State Cancer Hospital, Columbia, Mo., and the Los Angeles Tumor Institute, Los Angeles.

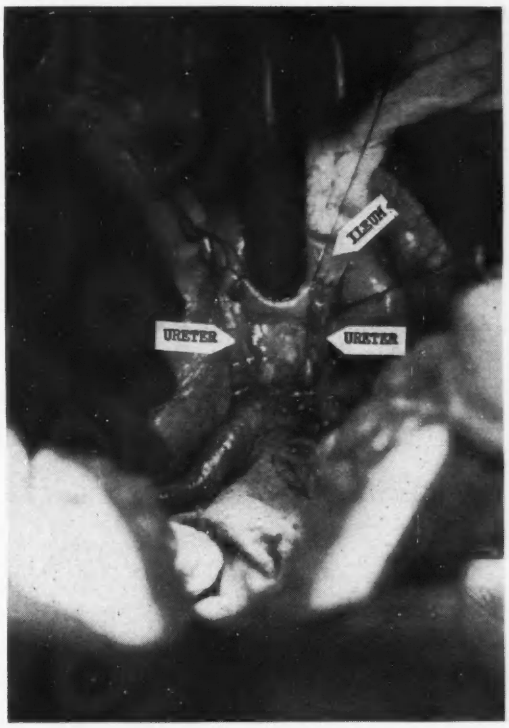

Figure 1.—The region of the sacral promontory with the uretero-ileostomies displaced upward to demonstrate the anastomotic site.

There were 37 cases for long-term observation postoperatively. The patients were examined frequently until they died or up to the time this report was prepared. Autopsy was not done in many of the cases in which the patient died, but owing to the frequency of examination, the cause of death—whether cancer or other cause—could definitely be determined in all instances. This was accomplished either by biopsy or x-ray examination, which provided concrete evidence of metastatic disease. The shortest period of postoperative observation in the series was three months and the longest was 60 months. The mean was 18 months. Only four patients in the group were observed for less than six months; and of these four patients, three died of persistence of the cancer for which they were originally treated in less than six months. The other patient was living at the time of this report. Eighteen of the patients died during the period in which the series was under observation. In 17 cases death was the result of surgical failure to control the neoplasm for which the patient was treated. One death was attributable to the urinary diversion. The patient was a man who had had pelvic exenteration for locally advanced adenocarcinoma of the rectum.

TABLE 3.—*Complications in 43 Cases in Which Ileal-Ureteral Anastomosis Was Carried Out*

Complication	Number	Incidence (Per Cent)
Stricture of ileostomy	6	14.0
Recurrent pyelonephritis	3	7.0
Stricture of ureter	3	7.0
Prolapse of ileostomy	2	4.6
Perforation of segment	1	2.3
Sensitivity to adhesive	1	2.3
Hyperchloremic acidosis	0	0.0
Uremia	0	0.0
Total	16	37.1

TABLE 4.—*Hydronephrosis and Hydroureter in Postoperative Intravenous Pyelograms*

	Number	Incidence (Per Cent)
Bilateral:		
Minimal	1	2.3
Moderate	2	4.6
Severe	3	7.0
Unilateral:		
Minimal	1	2.3
Moderate	1	2.3
Severe	2	4.6
Total	10	27.0

Rather than wear the usual bag which is glued to the skin, he insisted on wearing a Foley catheter in the ileal segment. This he connected to a leg bag which acted as a urinary reservoir. Forty-two months after the pelvic exenteration, the patient perforated the ileal segment with the catheter and, as a consequence, died. Autopsy was done in a distant city and a report forwarded to the author. At the time of autopsy there was no evidence of persistent cancer; the patient had died of a peritonitis following the perforation of the ileal segment.

Sixteen patients had nonfatal complications of the urinary diversion (Table 3).

Stricture of the ileostomy stoma occurred in six patients (Figure 2). This is not at all a serious complication, since the stricture is always located at the skin level. Such strictures are usually easily dealt with under local anesthesia as an office procedure. Stricture of the ureter occurred in three cases—in two cases at the uretero-ileostomy site, and in the other about five centimeters above the uretero-ileostomy, apparently owing to previous irradiation damage there. For operation to relieve stricture, hospitalization is necessary.

Recurrent pyelonephritis developed in three patients. These recurrent episodes of renal infection were on the whole readily controlled by chemotherapeutic agents; and during the course of follow-up, two of the three patients subject to recurrent attacks of ascending renal infection died as a result

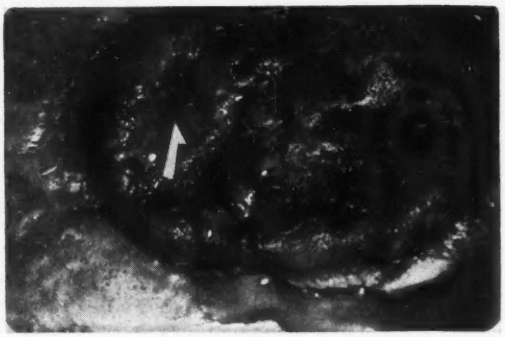

Figure 2.—A close-up view of stenotic ileostomy. To the left and above the center of the picture, a stenotic opening approximately 3 mm. in diameter may be seen.

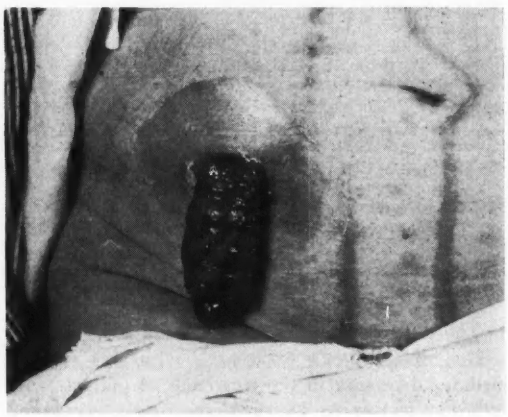

Figure 3.—Typical prolapse of an ileal segment.

of persistence of the primary cancer and generalized carcinomatosis.

In two cases prolapse of the bowel through the artificial anus occurred (Figure 3). In both cases surgical repair was effected. In one of these cases prolapse recurred twice before being successfully repaired. This complication does not affect the urinary diversion any more than prolapse affects the course of the patient who has had ileostomy because of ulcerative colitis.

Soon after operation, one patient had severe sensitivity reaction to the adhesive material used to hold the latex reservoir to the skin. Several days of hospitalization was required, but after the skin about the ileostomy was toughened, this sensitivity was controlled.

Renal damage as evidenced by changes in the intravenous pyelogram was noted in ten cases (Table 4). It should be noted at this point that of a total of ten patients with preoperative renal damage, as evidenced by intravenous pyelograms, eight were improved after the urinary diversion.

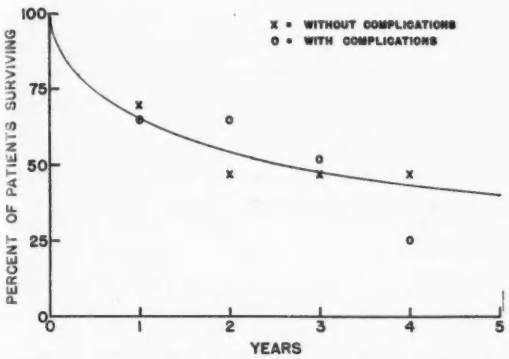

Chart 1.—Survival data on 37 of 43 patients who had ileal-ureteral anastomosis for urinary diversion. Data excludes five cases in which patient died in postoperative period.

In order to determine the degree to which these complications of urinary diversion into an ileal segment have affected the ultimate survival of these patients, accumulative survival rates were plotted (Chart 1). It is to be noted that a single curve can describe the final fate of patients with or without late complications referable to ileal segment diversion. In terms of numbers, the distribution of patients with and without complications was of about the same order of magnitude. This implies that failure of treatment of the malignant neoplasm rather than the urinary diversion limits the life of the patient.

Of 16 patients who had late complication of urinary diversion, four had preoperative evidence—changes in intravenous pyelograms—of involvement of the upper urinary tract. In the group without late complications, six had evidence of urinary tract involvement as determined in the same manner. Apparently preoperative involvement of the urinary tract does not contribute to the development of late complications of the urinary diversion but, rather, describes the advanced state of the primary disease.

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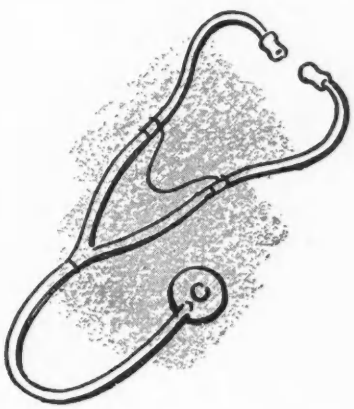

The Management of Allergic Patients

The Role of the Internist

SAMUEL H. HURWITZ, M.D., San Francisco

• There has been an increasing trend in the United States toward intensive specialization in allergic diseases. Whereas the tendency toward specialization has led to greater knowledge of the scientific aspects of allergic phenomena, it has somewhat diverted the specialists' attention from the many clinical problems that await solution.

Effective treatment of the allergic patient depends in no small measure on the broad viewpoint and clinical experience of the internist. This fact has been reemphasized by the growing awareness of the significance of the secondary or precipitating causes, such as climatic, nutritional, hormonal and psychogenic factors which influence allergic manifestations. Overemphasis on specialization in allergic diseases with their wide ramifications may defeat the main objective—a successful therapeutic result.

To meet this challenge, the internist should be trained in allergy and yet retain a broad approach to the more basic problems of internal medicine. This objective may be attained by certain modifications in undergraduate medical instruction in allergy. Postgraduate training sponsored by our national allergy societies affords internists an excellent opportunity to advance their knowledge of clinical allergy.

DURING THE past 25 years, we have witnessed an increasing trend in the United States toward specialization in internal medicine. The cardiologists, endocrinologists, hematologists and allergists have now taken their place with the subspecialists as detached workers in their several fields.

The intensive cultivation of the allergic field in the United States has been furthered by the organized efforts of our two national societies for the advancement of knowledge of allergic phenomena, and by the activity of the many regional and state organizations. This has led to valuable clinical and laboratory studies on allergic diseases.

Allergic phenomena are matters of moment in many basic sciences. Physiologists have made important contributions to knowledge of the part which autonomic innervation of smooth muscle plays in the production of symptoms, and pathologists have added greatly to knowledge of the tissue changes in allergic reaction. Immunologists and immunochemists, by their research, have made possible a clearer understanding of the mechanisms involved. It is obvious that the clinician who must devote his efforts to the diagnosis and treatment of allergic diseases has neither the time nor perhaps the training to aid in the solution of the more fundamental problems.

Whereas emphasis on specialization has added greatly to the science of allergy, it has to some extent diverted the specialists' attention from the many clinical problems which must be solved if success in treatment is to be achieved. It is for this reason that there has been a growing awareness during the past decade of the significance of the secondary or precipitating causes of allergic diseases. This has stressed the need for a broader clinical approach and the importance of the internist's role in the management of patients with allergic reactions.

The first classical descriptions of hay fever and asthma were given by clinicians in the early and latter part of the nineteenth century.[4] It is of historical interest that many of these careful observers had the diseases they so accurately described.

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John Bostock, an English physician and physiologist, was the author of the first clinical description of hay fever.[5] In 1819, he read a paper before the Royal Medical and Chirurgical Society of London on a "Case of a Periodical Affection of the Eyes and Chest"[2] in which he presented to the members the history and clinical symptoms of a seasonal disease which had troubled him since childhood.

Bostock, however, did not recognize that pollen was the cause of his symptoms. That pollen was an etiologic factor in seasonal hay fever was proved by the crucial clinical experiments of Charles Harrison Blackley of Manchester, England, and Morrill Wyman of Cambridge, Massachusetts. Blackley[1] first published his observations in a treatise entitled "Experimental Researches on the Causes and Nature of Catarrhus Aestivus (Hay Fever)"; and Wyman, in an exhaustive monograph on "Autumnal Catarrh,"[8] published in 1876, made the first noteworthy American contribution to etiologic knowledge with the observation of the association of hay fever and the pollen of ragweed.

The accuracy of the observations made by these investigators and the logical deductions from them are indeed remarkable, since their work was carried out before controlled experiment had come into general use in medicine.

Another clinical contribution of major importance was the publication in 1860 of Salter's monograph on "Asthma: Its Pathology and Treatment."[7] Asthmatic himself, Salter had excellent opportunity to study carefully his own symptoms and, in particular, the reflex phenomena which he believed to be, in many instances, the precipitating causes of the attacks. His description of asthma due to animal emanations, especially that caused by exposure to the domestic cat, should be read by every student interested in the subject.

In 1906, Clemens von Pirquet, distinguished for his work on serum disease, vaccination and tuberculosis, suggested the term *allergy* for the changed reactivity of the organism following the repeated introduction of pathogenic substances. His researches led to the development of new diagnostic methods for the study of tuberculosis in childhood. They also paved the way to knowledge of the pathogenesis of many other diseases, particularly those of allergic origin.

Another milestone in the development of the science of allergy was the publication in 1911 of Noon's paper on "Prophylactic Inoculation Against Hay Fever."[6] The successful therapeutic results he achieved by desensitization with pollen antigen stimulated intensive clinical and laboratory studies on the underlying causes of allergic phenomena and the mechanism of specific treatment.

The intensity of interest given to these experimental and immunologic studies during the half century after von Pirquet made his contribution, diverted attention from the many clinical problems which beset patients with allergic disease. The effective treatment of these patients depends, to a great extent, on the broad viewpoint and clinical experience of the internist. Too intensive specialization in allergic diseases, with their wide ramifications, may defeat the main objective, which should be a successful therapeutic result. For this reason the internist should be trained in allergy and yet retain a broad approach to the more basic aspects of internal medicine.

Undergraduate instruction in allergic diseases has been for the most part, inadequate, in view of the fundamental importance of allergic manifestations in the practice of medicine. Teachers of this subspecialty have made many practical suggestions in order to correct this deficiency. A plan found workable in some medical schools in the United States is to give instruction in subjects so widely ramified as allergy, as a part of the individual basic sciences.[3] Such a plan would lessen the trend, all too prevalent in our medical schools, toward overburdening the curriculum.

Thus a course in immunology and immunochemistry could include a discussion of sensitization in experimental animals and in man and of the fundamental mechanism of anaphylaxis and human hypersensitivity. The physiologist and the pathologist could devote some time to the physiologic and pathologic aspects of the allergic reaction and the pharmacologist to an evaluation of the common adrenergic and anticholinergic drugs, antihistamines and the adrenal corticosteroids in the therapy of allergic diseases.

These basic facts and theories may then be coordinated with the common clinical manifestations of allergic reaction, such as hay fever, asthma, eczema and urticaria. This integration of the subject could be achieved in a limited number of lectures and the presentation of clinical cases typical of the various kinds of allergic disease either in the outpatient allergy clinic or in the hospital wards. A qualified member of the teaching staff could carry out this assignment. He should possess not only training in internal medicine or pediatrics but also the essential clinical and technical experience in the diagnosis and treatment of allergic diseases. The latter may be acquired either by postgraduate instruction or work in an organized allergy department of a medical school or hospital. If one may judge by present-day trends, the internist in the future is certain to play a greater role in the management of the allergic patient.

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Vaginal Cytology

Results in 3,000 Consecutive Women with "Normal" Cervices

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• **Cytologic examination of 9,000 specimens of mucoid material taken from the cervices of 3,000 women who had no clinically observable vaginal abnormality was carried out. Sixteen of them had carcinoma, later proved by tissue examination. In 15 cases the lesion was epidermoid carcinoma of the cervix and in one was adenocarcinoma of the endometrium. Routine use of examination of mucoid specimens easily and painlessly obtained from the vagina should contribute substantially to a lower mortality from pelvic carcinoma.**

IN THE LAST 15 years cytologic examination of material from the cervix and vagina has become routine in most gynecologic clinics and in many private offices. The results in early diagnosis and prompt treatment of cancer of the cervix have helped to lower the mortality rate associated with this disease.

Although the literature contains many reports of the incidence of detection of carcinoma by cervical and vaginal smears, there is great variation in the data. In large series the range is from 0.9 per cent to almost 6 per cent of patients with proved carcinoma detected by this method. Obviously these data are colored by the type of practice involved and none are truly representative. Clinics dealing only with gynecologic patients have a higher rate because the patients examined have specific complaints referable to the pelvis. In general, reports from cytodiagnostic centers show relatively high proportions of diagnosis of cervical cancer, because most of the specimens sent in for examination are from patients with some clinical signs of cervical abnormality.

Data as to the number of carcinomas that would be found in routine examination of cervical material from an unselected cross-section of patients are still lacking. The criticism has been raised that such a screening procedure would be excessively costly, and that it would be far more practical to take mucoid material or tissue for biopsy only if the patients have signs or symptoms of abnormalities such as erosions, lacerations and cervicitis. The purpose of the present investigation was to determine just how many cases of carcinoma of the cervix would be missed if such a procedure were followed.

MATERIAL AND METHOD

In a medical group, routine screening by the Papanicolaou method was done on women over the age of 30 by the departments of obstetrics and gynecology, internal medicine, and surgery. Notes were made by the examining physician as to whether there was any apparent abnormality of the cervix. All cases in which the patient had erosion, lacerations, polyps or palpable abnormality were excluded from this series. Only those in which the cervix was considered normal were included. Nine thousand specimens from 3,000 consecutive cases of women with "normal" cervix and vagina are the material of this report.

Three specimens were taken from each patient. One was obtained by rotating a cotton tipped applicator in the endocervix, another by circumferential scraping of the squamo-columnar junction with a wooden Ayre spatula, and the third by gathering secretion from the posterior fornix on the opposite end of the spatula. All specimens were obtained after the insertion of a moistened vaginal speculum and before the usual bimanual examination with the lubricated gloved fingers. This avoided contamination of the specimens by vaginal jelly. The specimens were immediately placed in an ether-alcohol mixture and were later stained by a modified Papanicolaou procedure.

The age range of patients in the series was from 30 to 82 years. Specimens positive for cancer were found in an age range of 31 to 74 years.

No attempt has been made to include for discussion in this communication the proportion of false negative and false positive results. Nor were results in the present series compared with results in cross-sections of all patients regardless of the condition of the cervix. Statistics on these aspects are being prepared for later report.

In all cases in which the cytologic examination was positive for cancer, biopsy and curettage was done—repeatedly in many cases. Only cases in which carcinoma was proved by biopsy or curettage

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were included in the computation of results. Patients having metaplasia and the so-called "precancer complex" were regularly reexamined and if definite malignant changes developed, as identified in biopsy specimens, they were included in the group used.

RESULTS

Sixteen proved cases of carcinoma were found in the 3,000 women who had no visible or palpable evidence of any abnormality of the cervix—an incidence of slightly more than one-half of 1 per cent. Fifteen were epidermoid carcinomas of the cervix and one was an early endometrial adenocarcinoma. Five of the squamous cell carcinomas occurred in cervical stumps left following subtotal hysterectomies. In seven cases the lesion was noninvasive carcinoma in situ.

DISCUSSION

Further improvement in the mortality rate associated with cancer of the cervix depends in some degree upon diagnosis before the lesions have reached a clinically suspicious stage. Cytodiagnosis is of inestimable value in the detection of unsuspected cases of carcinoma of the cervix and uterus.

Traut and Benson said: "Biopsy is a *focused* cancer test, whereas the use of stained smears and films of aspirated fluid, employing criteria of malignancy is a diffuse biopsy method. Thus they can reveal the smallest cancers or earliest malignant tendencies in the uterine cavity, the cervical canal, or portio. Cancer cells shed more rapidly than normal elements, and the vagina forms a natural repository where they collect."

There is no limit to the number of specimens that can be obtained. The patient is not subjected to pain. Specimens may be obtained as often as desired. They give evidence earlier, and from a larger area, than does tissue biopsy. Obtaining specimens at routine intervals gives added incentive to the patient to have periodic examinations.

Examination of vaginal mucoid specimens is a screening or sorting procedure only. When results of cytologic examination are positive for cancer, biopsy and curettage are absolutely necessary. When results of tissue biopsy and of mucoid material do not agree, repetition at regular intervals is mandatory. It is typical that exfoliation of malignant cells occurs in "showers." Hence results of examination of one specimen may disagree with those on another specimen taken at a different time.

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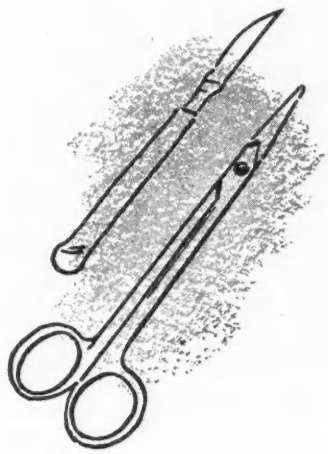

CASE REPORTS

Recurrent Meningitis Due to E. Coli, With Recovery

MAURICE AVENS, M.D., Los Angeles

A FIVE-WEEK-OLD Caucasian girl, admitted to the Los Angeles County General Hospital Communicable Disease Unit on March 19, 1956, had been perfectly well until she began vomiting after feedings two days before admission. On the day preceding admission, a high fever developed and the patient seemed to be in pain when her legs were moved. There was no history of diarrhea or upper respiratory tract infection and no known exposure to communicable diseases.

On admission, the pulse rate was 140, the respirations 36 per minute, the temperature 101.6°F. rectally, and the body weight 8 pounds. The patient appeared acutely ill and was fretful on extension of the legs. No abnormalities of the skin, the fontanels, the ears and throat or the lungs were noted. There were no signs of meningeal disease. A specimen of spinal fluid was cloudy and contained 5,900 cells per cu. mm.—31 per cent polymorphonuclear cells. One cubic centimeter of spinal fluid reduced six drops of Benedict's solution. There was a 3 plus reaction to a Pandy test. A Gram-stained specimen of the fluid showed Gram-negative rods. A culture of material swabbed from the throat on admission grew Alpha streptococcus viridans, Staphylococcus albus and diphtheroids. Cultures of blood and spinal fluid grew E. coli which were sensitive to streptomycin, aureomycin, chloramphenicol, terramycin, achromycin, neomycin and polymyxin. The blood urea nitrogen content was 15.0 mg. per 100 cc., carbonate content 20 mEq., and potassium 5.6 mg. per 100 cc. The hemoglobin content was 8.5 gm. per 100 cc. of blood, and leukocytes numbered 5,700 per cu. mm. —18 per cent polymorphonuclears.

The infant was treated with intravenous fluids containing potassium penicillin, chloramphenicol and adrenocortical extract, together with the usual vitamins. She also received by clysis 6 molar sodium lactate containing sulfadiazine and sulfamerazine. Five hours after admission, the pulse increased to 160 and the abdomen became tense. A series of epinephrine injections was given, a nasogastric tube was passed, and 0.25 cc. of Parenzyme (trypsin) was given intramuscularly every 6 hours.

In the succeeding days the infant improved clinically. Throughout the hospital course the urine was examined daily for sulfa crystals, and the pH of the urine was maintained on the alkaline side. In an x-ray film of the chest on March 12, the only abnormality was patchy density in the left upper lung. Lumbar puncture was attempted on March 13 but was unsuccessful. On March 17 lumbar puncture was successfully carried out and the pressure was 150 mm. of water. The fluid was clear and xanthochromic. It contained 36 cells per cu. mm.—5 per cent polymorphonuclears. One cubic centimeter of fluid reduced 7 drops of Benedict's solution. Reaction to a Pandy test was 1 plus. An electroencephalogram was unsuccessful because of the patient's moving and crying. Leukocytes in the blood numbered 12,000 per cu. mm.—60 per cent polymorphonuclears. On March 19, the hemoglobin was less than 7.5 gm. per 100 cc. of blood and leukocytes numbered 11,600 per cu. mm.—63 per cent polymorphonuclears. On March 22, the hemoglobin still was less than 7.5 gm. per 100 cc. and the leukocyte content was 8,800 per cu. mm. with 48 per cent polymorphonuclears. On March 23, a specimen of spinal fluid was clear. It contained 45 cells per cu. mm., none of them polymorphonuclear. One cubic centimeter reduced 3 drops of Benedict's solution, and the Pandy test reaction was 1 plus. The hemoglobin content was 7 gm. per 100 cc. of blood and leukocytes numbered 21,200 per cu. mm., 42 per cent of them polymorphonuclear cells. At this time 45 cc. of whole blood was infused through a vein in the scalp. The following day the hemoglobin was 9 gm. per 100 cc. An additional 30 cc. of whole blood was infused and on March 26 the hemoglobin was 10 gm. per 100 cc. Leukocytes numbered 10,800 per cu. mm.—52 per cent polymorphonuclear cells. On March 28, lumbar puncture was carried out and the fluid was clear with 33 cells per cu. mm., none of them polymorphonuclear. The sugar content was normal and the Pandy test reaction was 1 plus. Leukocytes in the blood numbered 9,700 per cu. mm., 36 per cent of them polymorphonuclear. Treatment was stopped on this day.

The child remained afebrile from March 12, 1956, until discharge and continued bright and alert. No neurological impairment was observed.

On April 6 lumbar puncture was attempted but

From the Communicable Disease Service of Albert G. Bower, M.D., Chief Physician, Los Angeles County General Hospital, Los Angeles 33.
Submitted August 10, 1956.

was unsuccessful. Leukocytes numbered 10,600 per cu. mm. of blood, 50 per cent of them polymorphonuclear. The patient was discharged April 7 with an appointment for an electroencephalogram in one month. No organisms grew on culture of any of the specimens of spinal fluid obtained during the stay in hospital with the exception of the specimen taken at the time of admittance.

On April 8 the parents returned to the Communicable Disease Unit with the infant, stating that the child had become irritable and vomited the evening feeding on the day she came home from the hospital. She had slept fitfully during the night and at 10:30 next morning the temperature was 102°F.

The patient was readmitted and the temperature at that time was 102°F., the pulse rate 142, and respirations 38 per minute. Except for slight engorgement of vessels in the posterior pharynx, no abnormality was noted in the ears, nose and throat. No nuchal rigidity or other meningeal signs were present. Lumbar puncture was attempted but was unsuccessful. Cisternal puncture was done and the fluid pressure was 110 mm. of water. The fluid was xanthochromic and it contained 1,232 cells per cu. mm.—60 per cent polymorphonuclear cells. One cubic centimeter of fluid reduced 7 drops of Benedict's solution. Reaction to a Pandy test was 1 plus. Hemoglobin content of the blood was 9 gm. per 100 cc. Leukocytes numbered 18,500 per cu. mm.—72 per cent polymorphonuclears. The urea nitrogen content was 24 mEq., carbonate 23 mEq. and potassium 6.1 mEq.

Chloramphenicol, streptomycin and sulfadiazine were given by vein and sulfamerazine by clysis. Two days later, on April 10, the child was reported to have had recurrent episodes of unconsciousness with upward-rolling of the eyes, each episode lasting 5 to 30 seconds. One such episode was accompanied by a tetanic convulsion. The temperature at this time was 100.8°F. rectally and the pulse rate 180. Chloral hydrate was given per rectum, which controlled the convulsive seizures. On April 11, the patient became afebrile and had no more convulsions.

A lumbar puncture was performed April 13, and the fluid was xanthochromic and "ground glass" in appearance. The pressure was 40 mm. of water and there were 49 cells per cu. mm., none of them polymorphonuclear. The sugar content was normal and the Pandy reaction was 1 plus. On April 16, the infant was given 150 cc. of whole blood in a vein in the scalp. Five days later the hemoglobin content was 14 gm. per 100 cc. of blood. Leukocytes numbered 6,100 per cu. mm.—24 per cent polymorphonuclears. The following day lumbar puncture was done and the fluid was clear. It contained 23 cells per cu. mm., none of them polymorphonuclear. The sugar content was normal and the Pandy test reaction was 1 plus. Therapy was discontinued and the patient remained afebrile and continued to gain weight. On May 15, lumbar puncture was done again. The fluid was clear, the cell content 8 per cu. mm., with no polymorphonuclear cells, the sugar content normal. There was faint reaction to a Pandy test. The hemoglobin content of the blood was 12 gm. per 100 cc., and leukocytes 6,300 per cu. mm., with 15 per cent polymorphonuclears.

No organisms grew on cultures of all the spinal fluid specimens obtained during the second period of hospitalization. The patient was discharged on May 16.

SUMMARY

A case of meningitis due to E. coli, with recurrence and recovery, is presented.

1200 North State Street, Los Angeles 33.

Tetanus with Complete Recovery

BARBARA DUVALL, M.D., Los Angeles

A SIX-YEAR-OLD Mexican boy fell while playing and struck his abdomen. Next day he began to have severe abdominal pain and rigidity. In the succeeding two days the condition became increasingly severe. Generalized stiffness developed and the patient could not open his mouth. He was then (four days after injury or three days after symptoms were first noted) taken to a physician who referred him to the Communicable Disease Unit of the Los Angeles County General Hospital on March 3, 1956, on suspicion of poliomyelitis, meningitis or neglected acute abdominal disease.

When the history was taken it was noted that the boy was accustomed to playing barefooted and had never received immunization of any kind.

The patient appeared to be acutely ill. He could open his jaws only about a half inch. There was pronounced abdominal muscle rigidity and stiffness of the neck, and moderate generalized muscular rigidity made it difficult to flex the arms and legs. In addition the patient had multiple small splinters and pieces of dirt ground into the skin of both hands and feet, an infected granulating lesion on the right great toe and another open granulating lesion on the left index finger.

A specimen of spinal fluid was obtained immediately. It was clear, contained 3 cells per cu. mm., one of them polymorphonuclear, and a normal amount of sugar. A Pandy test reaction was negative.

A diagnosis of tetanus was made on the basis of clinical evidence, and therapy was started within a few minutes after the patient's arrival. He was scrubbed with soap and water and skin and intravenous tests for sensitivity to tetanus antitoxin were carried out. Administration of 40,000 units of tetanus antitoxin in normal saline solution intravenously was begun. In addition 40,000 units of antitoxin was given intramuscularly in each buttock, 10,000 units around the left ankle, 10,000 units around the left wrist, and 20,000 units around the right ankle. Surgical debridement of the two larger

From the Communicable Disease Service of Albert G. Bower, M.D., Chief Physician, Los Angeles County General Hospital, Los Angeles 33.

Submitted August 10, 1956.

skin lesions was carried out. The patient, who had begun to have moderate contractions during the foregoing procedures, was sedated with chlorpromazine.

In the following days, intravenous fluids, supplementary vitamins and antibiotics were administered. Every three days 1,500 units of tetanus antitoxin was given to prevent sensitization. Contractions were satisfactorily controlled by a combination of chlorpromazine and chloral hydrate. On the sixth hospital day the patient was able to eat, and intravenous fluid therapy was stopped. On the twelfth hospital day sedation was tapered, and on the 26th day, when rigidity and contractions had completely ceased, it was discontinued.

On about the fifteenth hospital day the patient began sweating profusely. Slight epistaxis occurred from time to time. A cardiac murmur along the left sternal border was noted. On the twenty-third hospital day an urticarial rash, generalized adenopathy and irritability developed, and the temperature then ranged from 102° to 103°F. for nine days. An electrocardiogram, x-ray films of the chest, the antistreptolysin titer and results of liver function tests showed no abnormality. No organisms grew on a culture of blood. Relative lymphocytosis with about 25 per cent atypical lymphocytes was noted upon examination of specimens of the blood, but heterophil titers, repeatedly determined, were within normal limits. The symptoms were interpreted as serum sickness, a reaction to the tetanus antitoxin, which was then discontinued on the twenty-second hospital day.

Following this episode, the patient became afebrile and remained so. X-ray films of the spine showed no fractures, and the patient was discharged on the forty-eighth hospital day. The parents were advised that active tetanus immunization should be begun within the following six weeks.

1200 North State Street, Los Angeles 33.

Echinococcus Cyst with Intrabiliary Rupture

GEORGE D. LAVERS, *M.D.*, Tulare

ECHINOCOCCUS is an uncommon disease in California. Since many cases are asymptomatic, the present case, in which rupture into the biliary tract resulted in obstructive jaundice, is reported as a reminder of the existence of Echinococcus granulosus in California. This disease, as well as other "tropical diseases," is occurring with increasing frequency in subtropical and temperate regions. Since echinococcus is not a notifiable disease in California, data on the incidence are not available. Johnstone[2] expressed belief that the incidence is higher than is generally recognized, and he said that "apparently clinicians are not even suspecting the presence of the parasite." Information on the surgical complications of echinococcus cyst is rather scant in American textbooks and journals, the best reports having originated in other countries. When rupture of the cysts occurs it may be into the bile ducts, the general peritoneal cavity, the thorax, or the alimentary or urinary tract.[1,3]

Submitted August 6, 1956.

REPORT OF A CASE

The patient was a 27-year-old man of Mexican descent who had been born in Los Angeles and had lived in California all his life. He was first observed in the Tulare County Hospital in December, 1955, with a history of severe, cramping pain in the right upper quadrant of the abdomen, with jaundice and dark urine, for the preceding two weeks. In the three days before entering the hospital the patient had had chills and fever. At examination upon admittance to the medical service, pronounced icterus, tenderness in the right upper quadrant of the abdomen and enlargement of the liver were noted. The laboratory reported an icterus index of 54 units, total bilirubin content of 4.3 mg. per 100 cc. of blood. Hemoglobin content was 12.2 gm. per 100 cc. and leukocytes numbered 11,800 per cu. mm. The result of a serologic test for syphilis was negative. A cephalin cholesterol flocculation test was negative for liver impairment. The content of alkaline phosphatase, 15.8 mg. per 100 cc. of blood. Roentgen studies of the upper gastrointestinal tract showed

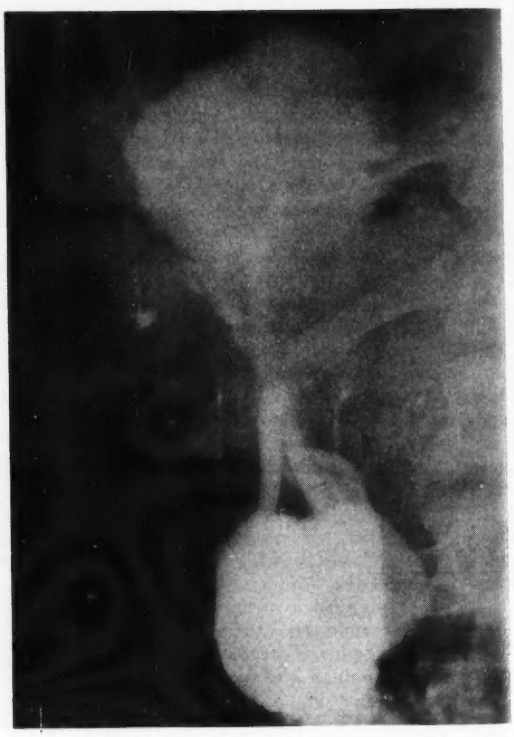

Figure 1.—Cholangiogram 25 days after operation. Note contrast medium in intrahepatic cyst.

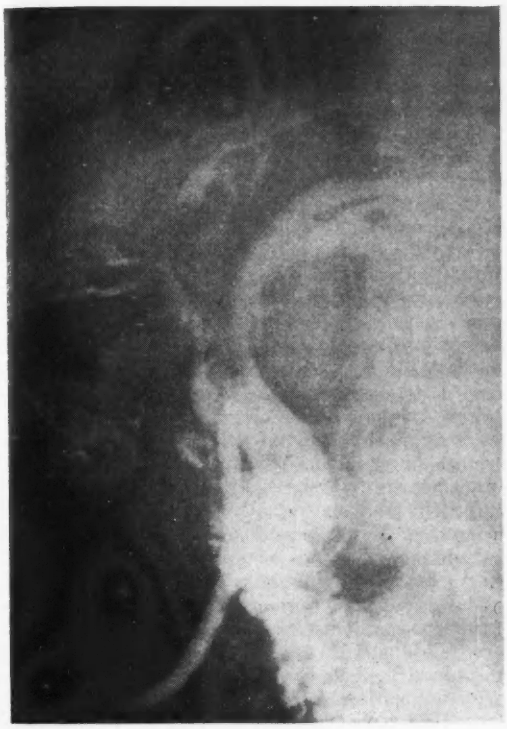

Figure 2.—Cholangiogram, four months after operation, showing return toward normal.

some compression of the lesser curvature of the stomach, evidently from the liver. The temperature ranged between 101°F. and 102°F. for three days and then became normal. The patient was treated with penicillin and was discharged after 12 days with a diagnosis of possible infectious hepatitis. Ten days later he returned because of fever and pain. This time the cephalin flocculation was 2 plus, thymol turbidity 18 units, and bilirubin 3 mg. per 100 cc. Biopsy of a specimen of the liver was reported as showing infectious hepatitis.

Pronounced jaundice continued and the patient had pain and recurrent fever. The temperature rose to 104°F. and the leukocyte content of the blood to 15,400 per cu. mm.

At operation the right lobe of the liver was observed to be practically replaced by a giant cyst. This cyst posteriorly had expanded anterior to the right kidney as a large, thin-walled mass. The common duct was approximately 4 cm. in diameter. It was opened and multiple daughter cysts of various sizes were evacuated from it. Then digital and instrumental exploration of the communicating cystic cavities in the liver was carried out. The main cyst was in the right lobe, but there were several smaller cysts in the left lobe. More than a liter of fluid and daughter cysts of varying sizes were removed and a large T-tube was left in the common duct at the conclusion of the procedure.

Pathologist's Report: The specimen was a large quantity of clear hydatid cysts, varying in diameter from 0.3 to 3 cm. Each hydatid presented a thin wall and was filled with clear, colorless fluid. Accompanying the specimens were irregular fragments of soft grayish yellow membrane, representing wall of the major hydatid cyst from the liver.

Microscopically the wall of each hydatid was observed to be composed of a thin hyaline membrane with serrated lining. In some of the sections through the hydatid, a few cross-sections of tapeworm larvae could be seen.

Diagnosis: Hydatid disease of the liver (Echinococcus granulosus).

Following operation, the septic condition very quickly subsided. As it was felt that daughter cysts were undoubtedly still present within the liver, the T-tube was irrigated daily and small cysts and cyst membranes continued to be passed. The cyst cavities shrank promptly (Figure 1). The T-tube was removed six months after operation* when cholangiograms showed an essentially normal biliary tree (Figure 2).

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Infectious Mononucleosis Complicated by Landry's Paralysis, Requiring Respirator Care

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THE SYNDROME of infectious mononucleosis was first described by Pfeiffer in 1889. He reported it as a disease of the lymph nodes of children and noted that constitutional signs and symptoms were mild. It was not until 1931 that the first reports of neurologic complications of infectious mononucleosis were made. Johansen[12] reported a case of serous meningitis with no glandular involvement and almost no abnormality in the spinal fluid. Epstein and Dameshek[3] noted a patient with stupor initially, then increased protein and cells in the cerebrospinal fluid and, two days later, splenomegaly and generalized lymphadenopathy. Atypical lymphocytes were observed in the blood. The patient was perfectly well six weeks after the onset of the illness.

Since these reports, there has been an increasing number of reports describing neurologic complications of infectious mononucleosis or glandular fever.

*When last observed, 13 months after operation, the patient was entirely asymptomatic. Upon physical examination no abnormalities suggesting recurrent or persistent trouble in the biliary tract were noted.

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Bernstein and Wolff[1] tabulated 34 such reports in the literature from 1931 to 1947 as follows:

	Cases
Serous meningitis	4
Meningitis	10
Encephalitis	4
Meningoencephalitis	4
Meningoencephalitis and polyneuritis	7
Peripheral neuropathy	6
Optic neuritis (with papilledema without increased cerebrospinal fluid pressure)	1

Many investigators have emphasized that some of the "idiopathic" acute nervous system disorders may be associated with infectious mononucleosis, as are many cases of "aseptic meningitis." Furthermore, there may be leukopenia early, then a normal content of cells in the blood or leukocytosis with or without a relative lymphocytosis, but with atypical lymphocytes seen at some time during the course of the illness. Paul and Bunnell's description of the heterophil agglutination test in 1932 has helped immeasurably in the clarification of many of these obscure neurologic syndromes.

The majority of neurologic complications of infectious mononucleosis occur in adults. It has been observed that, even in epidemics of infectious mononucleosis, such complications develop in less than 1 per cent of patients; and in males more than in females. There may be changes in the cerebrospinal fluid without any neurologic signs whatsoever. On the other hand, acute neurologic effect may occur without demonstrable change in the cerebrospinal fluid. Bernstein and Wolff[1] stressed that complete recovery from neurologic complications in infectious mononucleosis occurs within a few days to several months in 85 per cent of all cases. However, the spinal fluid may remain abnormal for a longer period of time.

Attesting that infectious mononucleosis is not an innocuous disease and that neurologic forms may leave residual impairment, Motto[17] described a case in which a patient, with encephalitis due to infectious mononucleosis, had nystagmus and right facial paralysis 12 months after the acute phase of the disease. Bernstein and Wolff noted mild motor aphasia and difficulty in concentrating as permanent residual damage. Lawrence[14] reported that respiratory paralysis was the cause of death in seven of 16 fatal cases of infectious mononucleosis.

These reports stress the necessity for hospitalizing such patients where immediate respirator care is available. The complications may progress very rapidly; in a case reported by Durfey and Allen,[2] impairment progressed from monoplegia to complete quadriplegia with bulbar paralysis in a very short time. The case reported herewith is another example of the urgency of such precautions.

Many bizarre neurologic forms of infectious mononucleosis have been reported in the literature. Green[8] described a case of acute hemiplegia and aphasia in which the spinal fluid was completely normal. No abnormal cells were observed in the blood until two weeks after onset of the illness, when atypical lymphocytes were seen. An elevated changing heterophil titer was also noted. Geliebter[7] in 1946 described, for the first time, neurologic infectious mononucleosis in a child. The patient was a ten-year-old girl with lymphadenopathy, malaise and vomiting. There were no meningeal signs, but a lumbar puncture was carried out and the spinal fluid contained 9 mononuclear cells per cu. mm. and total protein of 400 mg. per 100 cc. Diplopia and muscular weakness followed. Poliomyelitis was considered at one time, but a changing heterophil agglutinin titer clarified the diagnosis. Walsh and co-workers[22] reported encephalitis from infectious mononucleosis in an eight-year-old boy. They also report neurologic infectious mononucleosis in an 18-month-old child, the youngest patient of record to have neurologic complications. Cerebellar symptoms also occurred in both of these patients. Walsh and co-workers emphasized that neurologic signs and symptoms may occur in any sequence with relation to other clinical evidence of infectious mononucleosis, or even without any other symptoms. Many investigators have reported neurologic complications concomitant with, days to weeks before or after other clinical manifestations of infectious mononucleosis. Walsh and co-workers further stressed that leukocytosis is not uncommon early and that, in severe neurologic cases, changes in the blood tend to be late. Bercel noted electroencephalographic abnormalities in all of five cases of neurologic infectious mononucleosis observed by him.

Ream and Hessing[19] reported a case ushered in by psychotic manifestations after a week of tenderness of lymph nodes. An electroencephalogram in this case was decidedly abnormal. Cheyne-Stokes respiration and aphasia were noted later. Kalmansohn and co-workers[13] in 1953 reported the sixth known case of coma complicating infectious mononucleosis. In the case reported it was especially interesting because the patient was 49 years of age, had no symptoms of neurologic disease and had permanent residual personality changes of considerable degree. Furthermore, there was no clinical evidence of infectious mononucleosis. However, the spinal fluid protein content was elevated and an elevated changing blood heterophil titer was reported.

An especially interesting form of neurologic infectious mononucleosis is the so-called "Guillain-Barre" syndrome. Guillain, Barre and Strohl in 1916[9] described cases of acute polyradiculoneuritis with pronounced increase in cerebrospinal fluid protein content without increase in the number of cells. This change in the spinal fluid was termed "albuminocytologic dissociation." Their criteria for the diagnosis of the syndrome were: Albuminocytologic dissociation in the cerebrospinal fluid and preponderance of motor weakness over sensory. They reported the prognosis favorable, usually with complete recovery.

In 1936, Guillain[10] stressed increased spinal fluid protein content, reporting 1,000 to 2,000 mg. of total

protein per 100 cc. as the usual finding. However, in 1937, at a symposium in Brussels, he withdrew many of his previous diagnostic criteria. Now it is conceded that hyperalbuminosis of the cerebrospinal fluid may frequently be absent in the early stages, and that it is due to local factors, such as vasodilatation and partial block to drainage of the cerebrospinal fluid due to edema and swelling of inflamed nerve roots. In addition, the outcome of this syndrome is not always benign; in 26 of 126 cases of the syndrome collected from the literature by Fox and O'Conner in 1942, the patient died. In 1949, Haymaker and Kernohan[11] concluded that there was no essential difference between the radiculoneuritis of Guillain, Barre and Strohl, and that of Landry's paralysis; they suggested the name Landry-Guillain-Barre syndrome to emphasize the possibility of fatal outcome. Raftery and co-workers[8] emphasized that evidence points to a virus as the etiologic factor in this disease, with or without a preceding respiratory tract infection. In only three of the 34 cases of the Guillain-Barre syndrome he reviewed did the patient have infectious mononucleosis; seven had upper respiratory tract infections and three had the influenzal syndrome. The remainder had no preceding illness. Garvin[6] noted that the Guillain-Barre syndrome is one of the rarer manifestations of neurologic infectious mononucleosis. Kalmansohn[13] emphasized that, in albuminocytologic dissociation of the cerebrospinal fluid, infectious mononucleosis must be differentiated from infectious neuronitis, poliomyelitis, central nervous system tumors and diabetic neuropathy. The Guillain-Barre syndrome is but one of many postinfectious encephalomyelopathic conditions.

In the few cases of neurologic infectious mononucleosis in which postmortem examination has been done,[8] engorgement of veins and capillaries of the meninges, with infiltration by mononuclear cells into the anterior nerve roots at all levels was observed. Perivascular hemorrhages, mild ganglion cell disease, moderate infiltrations by inflammatory cells in meninges and neuraxes and invasion of posterior roots and spinal ganglia have also been reported.

REPORT OF A CASE

A 14-year-old Caucasian girl was admitted to the Communicable Disease Unit of the Los Angeles County General Hospital on March 24, 1956. Two weeks previously she had had an upper respiratory tract infection with fever, nausea and headache. In four days the patient became entirely asymptomatic without treatment, and according to the physician who had attended her, there had been no abnormality in the pharynx and no splenomegaly or adenopathy. Three days before admittance, the patient began to complain of double vision and right-sided weakness. At that time leukocytes numbered 15,000 per cu. mm. of blood—84 per cent lymphocytes, 34 per cent of them being atypical. No abnormality was noted in the urine. A heterophil agglutinin titer of 1:3,000 after adsorption was reported at this time. The spinal fluid pressure was within normal limits. The fluid was clear; it contained 1 mononuclear cell per cu. mm. and the protein content was 8 mg. per 100 cc.

Two days before admission, the patient complained of stiffness of the neck. She was reexamined by the physician, who noted decreased reflexes in the left side of the abdomen and of the right knee and right ankle, in addition to nuchal rigidity. The patient was then given 40 units of zinc corticotropin (ACTH) intramuscularly daily on March 22, 23 and 24. On the day of entry to the hospital, the patient was reexamined and pronounced weakness of all four extremities and slight bulbar weakness were noted. She was, however, eating and drinking without difficulty.

Upon admittance the rectal temperature was 99.6°F, the pulse rate 100 with rhythm regular, the blood pressure 120/90 mm. of mercury, and respirations regular at the rate of 16 per minute. The patient was in acute distress, with an indistinct nasal voice and difficulty in maintaining respirations, which were shallow. The skin was normal. There was decided ptosis of the left eyelid, but the pupils were normal. Cough and gag reflexes were extremely poor but there was no pooling of pharyngeal secretions. A slight inflammation of the pharynx was noted, but no exudate. The intercostal muscles were completely paralyzed and both diaphragms were weak. There were no meningeal signs or adenopathy. There was question as to whether the spleen was enlarged; it was palpated by one examiner 1 to 2 fingerbreadths below the left costal margin.

Upon neurologic examination, complete left ophthalmoplegia, right external rectus paralysis, bilateral peripheral facial paralysis, poor gag reflex, and deviation of the protruded tongue to the left were noted. Sensations of pain and touch were apparently intact, and there was no demonstrable loss of position sense. Almost complete quadriplegia was noted, more on the right, with all muscle groups involved. The abdominal muscles were very weak, as were the diaphragms. The intercostal muscles were completely paralyzed, and the neck muscles were very weak. Biceps, triceps, knee and abdominal reflexes could not be evoked on either side. The ankle jerk was absent on the right and weak on the left. There were no pathologic reflexes.

Laboratory data

Results of laboratory tests were as follows:

March 24: The hemoglobin content of the blood was 14.2 gm. per 100 cc. Leukocytes numbered 8,500 per cu. mm.—56 per cent polymorphonuclear cells and 44 per cent lymphocytes, 11 per cent of the lymphocytes atypical. The cerebrospinal fluid was clear, contained no cells, a normal amount of sugar and gave negative reaction to a Pandy test. Blood urea nitrogen was 17.0 mg. per 100 cc., carbon dioxide combining power 26.0 mEq. per liter and potassium content 4.1 mEq. per liter. Vital capacity

was 700 cc. (normal for the patient was 2,500 cc.). Tracheotomy was done an hour after admission, and considerable pooling of pharyngeal secretions was noted. The patient was then placed in a tank type respirator and she did fairly well. An electroencephalogram was reported normal.

March 26: The hemoglobin was 12.0 gm. per 100 cc. Leukocytes numbered 9,000 per cu. mm.—37 per cent lymphocytes (11 per cent atypical), 2 per cent monocytes, and 61 per cent polymorphonuclear cells. The heterophil agglutinin titers were 1:7,168 before absorption and 1:3,584 after absorption with guinea pig kidney. (Ten days later, corresponding titers were: 1:7,168 before absorption and 1:1,792 after guinea pig kidney absorption.) The cerebrospinal fluid heterophil titer was reported as negative. The fluid contained 1 mononuclear cell per cu. mm., a normal amount of sugar and total protein of 40 mg. per 100 cc. There was 1 plus reaction to a Pandy test. Protein-bound iodine was 7.5 micrograms per 100 cc. of blood, cholesterol 145 mg. per 100 cc. and the I^{131} uptake was 9.6 per cent. X-ray films of the chest (taken March 26 and 28) were normal. Urine cultures grew gamma streptococcus and Staphylococcus albus.

April 4: Bromsulfalein retention after 45 minutes was nil. Thymol turbidity was 4 units; alkaline phosphatase, 3.5 Bodansky units; clotting time normal.

The patient improved rapidly. On March 29 the speech was noted to be improved. On April 1 the facial paralysis was less noticeable, and the patient was able to move both upper extremities for the first time. By April 17 she could be out of the respirator for eight hours daily and nine days later she had no further need of it.

On April 15 the protein-bound iodine content of the blood was 11.6 micrograms per 100 cc. A culture of the urine on that date again grew gamma streptococcus and Staphylococcus albus.

The patient was discharged on May 23, two months after admission. There was then no significant muscular weakness or other residual impairment, and she was walking fairly well. An encephalogram showed no abnormality. The final diagnosis was infectious mononucleosis with encephalomyelitis (and Landry's paralysis). The patient was given 20 cc. of gamma globulin intramuscularly on the day of admission, and 2,000 micrograms of vitamin B_{12} daily intramuscularly. Otherwise, treatment was entirely symptomatic.

DISCUSSION

The Paul-Bunnell, or heterophil agglutinin test is of especial importance in the diagnosis of infectious mononucleosis, but in a large proportion of cases elevation of titer does not occur. Raftery and co-workers[18] observed that the highest incidence of elevated heterophil agglutinin titer occurred in the second week of the disease, but even at that period there was no significant elevation in 40 per cent of proved cases. After the third week of the illness, elevation of titer occurred in less than 50 per cent of proved cases. Observation of atypical lymphocytes in a specimen of blood often is the only clue to the diagnosis, as in the case presented by Librach.[15] Since a heterophil agglutinin titer of 1:7 to 1:56 before absorption occurs in 80 to 90 per cent of normal persons, differential absorption is often of great help in differentiating infectious mononucleosis from normal states and from serum sickness (in which the titer may be quite high). The differential is as follows:

Normal serum—Absorbed by guinea pig kidney.

Serum from person with serum sickness—Absorbed by guinea pig kidney and beef red blood cells.

Serum from person with infectious mononucleosis—Absorbed by beef red blood cells, but *not* absorbed by guinea pig kidney.

However, according to Raftery[18] the titer of agglutination may vary because of variations in the sheep red blood cell suspensions used, not all sheep having blood of the same value. Moreover, in many cases serum from normal persons contains cold agglutinins for sheep red blood cells. Therefore, the test tubes used in performing the test should be warmed gently. Serial titration tests are especially useful in the diagnosis of infectious mononucleosis.

In 1948, Silberstein and co-workers[20] described the phenomenon of the presence of heterophil antibodies in the cerebrospinal fluid of patients with neurologic forms of infectious mononucleosis. Many investigators since then have not been able to verify the findings, although a few have. Silberstein described a positive qualitative heterophil reaction, but it remained for Freedman and co-workers[5] to describe a positive quantitative heterophil agglutinin titer of 1:28 in the spinal fluid of a patient observed by them. They emphasized how insensitive this test is when done on the spinal fluid, the blood heterophil titer concurrently being much higher.

The differential diagnosis of lymphocytic meningitis and neurologic infectious mononucleosis without lymph node involvement is often puzzling, but can be resolved, as was emphasized by Tidy,[21] by serial heterophil titration tests and observation of "Downey" cells in specimens of blood. Librach[16] urged that in all cases presumptive of poliomyelitis, serial heterophil tests and cytologic examination of the blood be carried out with infectious mononucleosis in mind. Moreover, the disease cannot be considered limited to persons of a particular age group: Fiese and co-workers[22] reported a case of neurologic infectious mononucleosis in a 58-year-old man, and Walsh[22] a case in an 18-month-old child.

The case presented in this report is especially interesting from several aspects:

1. The almost complete lack of clinical symptoms pointing to infectious mononucleosis. (The diagnosis might have been missed had the physician not ordered the necessary blood studies.)

2. The completely normal cerebrospinal fluid in the face of such extensive neurologic involvement.

3. Speculation as to the role corticotropin might have had in the course of the disease.

4. The sudden and extremely rapid severe involvement of practically every voluntary muscle group in the body, without apparent sensory involvement.

5. The extremely high heterophil agglutinin titer in the serum concomitant with "negative" titer in the cerebrospinal fluid.

6. The necessity for the use of a respirator for one month during the course of the illness.

7. The complete recovery of the patient in a period of two months, without residual effect.

Fiese and co-workers[4] used cortisone in treatment and speculated on the effect the drug may have had on the rapid recovery of the patient. However, they acknowledged the possibility that spontaneous recovery would have occurred as rapidly.

CONCLUSIONS

With the exception of bacterial meningitis, infectious mononucleosis must be considered in every acute neurologic syndrome whether or not there are changes in the cerebrospinal fluid—in patients of any age. Clinical manifestations such as enlarged lymph nodes, exudative pharyngitis or splenomegaly may be entirely absent throughout the course of the disease. The only clue to the diagnosis may be an elevated heterophil titer, or the presence of atypical lymphocytes or "Downey" cells in the blood. Leukocytes may be increased in number and the cell differential abnormal, but not necessarily.

Emphasis should be put upon the fact that the condition of patients with neurologic infectious mononucleosis may progress extremely rapidly—in a period of hours or days. These patients should be observed constantly in a hospital where tracheotomy and respirator care are instantly available.

The use of cortisone or corticotropin (ACTH) for treatment of patients with undiagnosed acute neuropathic conditions may be dangerous.

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Contact Ulcer of the Larynx

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THERE IS MUCH CONFUSION among laryngologists as to the etiology of contact ulcer of the larynx. Jackson[1] noted that the disease is often mistaken for some other condition. Contact ulcer has been attributed to constant or severe over-use of the voice and to environmental, occupational or habitual exposure to dust, grit, smoke or chemical irritants.

While it is true that the larynx reacts very sensitively to adverse conditions that put a strain on it either through local irritants or by undermining the general physical condition, contact ulcer in the strict sense of the word does not usually occur unless an element of emotional stress is present. Emotional upheavals may influence the biochemical changes taking place in the larynx, thus making the vocal cords a prey to pathological changes. Moses,[2] in an article titled "Vocal Cord Neurosis," said that contact ulcer had too long been considered the result of abuse of the voice, and he expressed belief that allergic sensitivity plays an important role. He cited the case of a singer with a normal larynx who developed a large

contact ulcer on the typical location, posterior end of the left vocal cord, the day before a concert.

While it is almost impossible to draw boundaries between the functional and organic vocal diseases, the personality, the drives, the emotions of the patient are factors that may help a physician to formulate the proper diagnosis and treatment. The following is a case in point.

REPORT OF A CASE

A man, then 30 years of age, upon emigration to the United States in 1929 experienced insurmountable emotionally charged difficulties. It was then that he felt for the first time that something was wrong with his throat. The specialists he called on advised tonsillectomy, which was performed in 1931. The condition was not relieved, however, and in the meantime the difficulties persisted and even multiplied. In 1934 a biopsy of tissue from the larynx was done but no abnormality was noted. The patient remained under observation and treatment by many physicians of different schools without improvement. In 1952 another biopsy specimen was removed, this time from the site of a granuloma, but it was negative for malignant change. In 1953 the patient spent a month at a medical center in Tucson, Arizona, remaining completely silent and undergoing heliotherapy. There was no improvement.

Having done extensive research work in the field of laryngeal tuberculosis, the patient could make knowledgeable examination of his own vocal cords. This he did daily. To facilitate the interpretation of observations, he used a modified hemoglobin colorimetric scale by which color changes were given a definite numerical value.

He noted some anatomical changes in the course of these daily inspections—first engorgement of the vessels in the larynx, then diffusion of redness. At no time was any pachydermatous thickening of the vocal cords observed. At times he noted unilateral perichondritis with ulceration on both local processes, the ulcer on the right side appearing and disappearing, but that on the left always present. Finally, while he was immersed in studying his own case and trying in every way to cooperate with physicians treating him, his difficulties, which had lasted so many years, suddenly came to an end—and with their passing, the emotional torment they entailed was dispelled. Thereupon all the subjective and objective symptoms of contact ulcer ended also.

In looking back over this case, Knight's admonition comes to mind: "Let each patient then be studied as a human being in distress whose manifestations of illness can be understood if enough can be learned about him and who can be treated with a therapeutic program which utilizes this comprehension rather than be viewed as a stranger with annoying complaints and troublesome symptoms to be immediately subjected to strong-arm purging methods."

SUMMARY

The cause of contact ulcer is very little understood, but emotional factors may underline the disease. Awareness of these factors may lead to more rational and successful treatment. A case report stresses this point.

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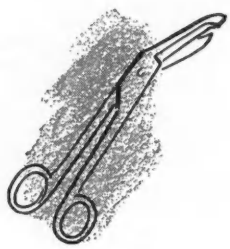

California MEDICINE

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EDITORIAL

Physicians vs. Poliomyelitis

PHYSICIANS—those in private practice and those in public health work—have demonstrated in the past six weeks their basic devotion to the betterment of human health. The rallying point has been the nationwide campaign to secure poliomyelitis vaccinations of all people under age 40.

The surge of response to the challenge of poliomyelitis has been so strong throughout the country that newspapers in all areas have blossomed out with editorials, cartoons and special articles in praise of the medical profession which many editors had previously been inclined to criticize.

Behind this movement lies the planning of national authorities who calculated, in the fall of 1956, that sufficient evidence was on hand to prove the safety and the effectiveness of the Salk vaccine and that, for the first time since the vaccine was introduced, sufficient supplies could be obtained to do a really mass job of inoculating people.

With this planning as basis, the American Medical Association called a meeting—on rather short notice—on January 26 and called the roll to find medical association representatives present from 48 states, the District of Columbia, Hawaii and Alaska. The meeting proceeded rapidly to the unanimous conclusion that now is the time to vaccinate people against poliomyelitis.

Most widely quoted statements from this meeting were those by Doctor Jonas E. Salk, developer of the vaccine, and Doctor George F. Lull, secretary of the American Medical Association. Doctor Salk referred to the present opportunity to deal poliomyelitis a body blow, and Doctor Lull commented that this was medicine's finest opportunity to demonstrate its dedication to the public service.

Currently, newspaper clippings from all parts of the country attest the admiration of editors for the stand medicine has taken. It is obvious that medical societies throughout the United States have taken the poliomyelitis program seriously and have used their organizational skills and techniques to see that a good job is done.

At home, the Council of the California Medical Association voted without dissent to cooperate with public health authorities to work for the vaccination of all Californians under age 40. Details of accomplishing this objective were left to the discretion of the county societies and a meeting of county executive officers has demonstrated the fact that the local societies have lost no time in setting up their own plans, rolling up their sleeves and going to work.

By and large the county-by-county approach to this broad program has been to cooperate in public mass vaccination programs, to encourage private groups to bring out their members for poliomyelitis vaccination and to urge private patients to visit their own physicians for inoculation. In several counties the local society members have adopted low fees for this service as a means of encouraging patients to make appointments.

With all the enthusiasm engendered for this program, it will be especially disappointing to meet stumbling blocks. However, such obstacles must be anticipated in any program of this magnitude. Already there are reported shortages of vaccine in commercial channels, a situation which is being met by asking the more northern areas of the country to defer to the earlier poliomyelitis seasons in the more southern sections and to delay their own programs until vaccine production and distribution can catch up with the tremendous demand created by the nationwide program.

California, with some 6,000,000 citizens eligible to participate in the plan, is bound to have some setbacks due to vaccine shortage, local inertia or other causes. However, if a large proportion of

eligible recipients end up with the protection offered by the vaccine, a good job will have been done and the ultimate elimination of poliomyelitis will be a foreseeable goal.

The zeal with which the campaign has been attacked in nearly all parts of the state argues for a splendid aggregate result. The county medical societies and their officers and members are to be congratulated on their performance. Bouquets are also due the state, county and local health officers who have made their offices the focal point in the district-by-district campaign and have provided invaluable leadership.

Legislative Time Again

WITH THE RECONVENING of the California State Legislature in the second portion of its bifurcated session, the picture of prospective medical legislation begins to clear. The five weeks' interval between the initial bill-introduction meeting and the current bill-consideration session has provided the time needed for analyzing and evaluating the myriad proposals tossed into the gristmill of the state's lawmakers.

The record shows more than 7,000 proposals put before the 120 men and women who make up the two houses of the Legislature. Medicine ordinarily expects about 10 per cent of these measures to have some bearing on the public health or the practice of medicine; this year the percentage seems to be a little less but there are still some 450 bills which will bear watching.

Among these are the perennial proposals to grant rights to selected individuals on the basis of legislation rather than education. These "fringe" bills would set up new examining and licensing boards, would broaden the legal scope or practice of some persons already given a limited license or would, in effect, legalize a change in name for some practitioners who apparently would seek this means of getting out from under an appellation which their predecessors valued highly but which has become burdensome over the years in the face of experience. Typical of this last group is the biennial proposal to license "naturopaths," a so-called profession which, from its roster of sponsors, would appear to be an offshoot of chiropractic.

Examples of what the public would face if "naturopathy" came into legal existence in California have been furnished by other states which have succumbed to the blandishments of the promoters of this "science" and have licensed them to practice, only to regret that decision within a few years and rescind the privileges already granted. A current report from Florida, one of the strongholds of this group, quotes the state narcotics inspector as stating that "if there are, or ever were, any schools offering courses in naturopathy other than diploma mills . . . it is a well-guarded secret . . ."

Another group seeking establishment of its own board for licensure or certification is the psychologists' organization, composed of Ph.D.s who wish to gain official recognition of their training and background through legal means. While their motives appear to be lofty and their training of the best, it has been shown in other states that certification as a psychologist inevitably leads to the interpretation of certification as licensure. And such a license treads on, if not over, the border of psychiatry. Medicine has never objected to official recognition of these trained people but it does believe that their practices should be considered as ancillary to the medical practice of psychiatry or other specialties and that, therefore, the psychologists should come under the examination and certification procedures of the Board of Medical Examiners.

In the field of pharmacy, more than 100 bills have been introduced. Many of these are simply technical amendments to permit more efficient administration of the law. Others are more directly aimed at physicians by adding mandatory requirements for the handling of dangerous or hypnotic drugs, a question on which medicine and pharmacy have disagreed in the past. It is interesting to note that dentistry has also been singled out as a group over which pharmacy officials would like a tighter rein, despite technical and economic factors which make some of the proposed bills appear almost ludicrous. Likewise, it is interesting that of more than 100 bills in the hopper, only eight have been introduced in behalf of the organized pharmacy profession and only 16 for the State Board of Pharmacy. The others have come from a variety of sources, some of them a little obscure.

One measure which has already caused a rash of opposition from certain sources is the so-called cancer quack control bill. The California Medical Association has embraced this bill as a co-sponsor and has watched with interest the adherents of Hoxsey and others attempt to kill the bill before it is even heard in committee.

This bill would provide a board, functioning in the State Department of Public Health, which would have authority to demand samples of drugs or devices claimed to be of value in cancer therapy and have such items scientifically tested in impartial laboratories. If such investigation proved the items worthless in treating cancer, the board would have authority to call the attention of state licensing authorities to the continued use of the products by licentiates of the respective boards. Only the licensing bodies would have punitive powers. This measure

promises to stir up a cloud of controversy, with science arrayed on one side and the proponents of testimonial cancer cures on the other.

As the Legislature gets under way in the next few weeks, additional reports will be forthcoming on the status of many individual proposals now under consideration. Meanwhile, there is every indication that medicine again faces a host of unwanted legislation and must continue to keep its guard up. Fortunately, the legislative forces of the C.M.A. are established on firm ground. Their vigilance and their performance may be counted upon without question.

Letters to the Editor . . .

To the Editor:

AFTER READING Dr. Ian Macdonald's reply to my protest against a section of the Cancer Commission's manual dealing with the question of a trial of androgen in refractory prostatic carcinoma [CALIFORNIA MEDICINE, March, 1957, page 189], I still cannot agree. Will you not, therefore, let me present factual data in support of my dissent:

Huggins, Stevens, and Hodges, in 1941[1] demonstrated that castration or estrogen therapy produced important palliation in prostatic carcinoma. They also studied the effects of androgen and found that it aggravated the tumor. Widespread investigation since that time has corroborated their findings. I have personally observed several patients subjected to androgen, to which most of them responded with increased pain from their metastases and sometimes with an aggravation of urinary symptoms or the appearance of a hemorrhagic diathesis. In one case, the drug appeared to have no effect whatsoever. In those patients made worse by androgen, the difficulties of palliation appeared increased despite withdrawal of the drug.

Tagnon and co-workers,[2] in a study of the bleeding tendency sometimes seen in advanced prostatic carcinoma, controlled bleeding due to prostatic fibrinolysis by giving estrogen. In one case, bleeding could be produced regularly by administering androgen. In four other cases, the experimental use of androgen had to be stopped because of aggravation of other symptoms. Whitmore, et al,[3] studied the effects of testosterone administration to more than twenty patients with advanced prostatic carcinoma. In two-thirds of these patients they observed neither subjective nor objective changes of any sort, but in the others, there was an unfavorable response. Scott[4] gave testosterone to three patients with advanced prostatic carcinoma in a carefully controlled study. Two patients appeared to be improved. Scott did not recommend that androgen be given in this disease but stated that further research would be of interest.

Because of Scott's report, and because a member of the Cancer Commission wrote me that he believed new information would show androgen to be valuable, I remained in doubt. In order to obtain an up to date and impartial opinion I wrote the A.M.A. and promptly received an answer from their urologic consultant which was later published in the *Journal of the American Medical Association*.[5] He stated, "There is no evidence to show that a cautious or any other type of trial of androgenic hormone is justifiable in patients with carcinoma of the prostate resistant to estrogen. A number of years ago, an occasional patient was found to respond temporarily in general health to large doses of androgen when suffering from carcinoma of the prostate with multiple metastases. The brevity of this improvement was emphasized by rapid dissemination of the disease and subsequent death."

The danger of aggravating the disease in late stages by androgen appears to outweigh any hope of control or palliation. Although cortisone[6] may be helpful to patients refractory to castration and estrogens, testosterone should be withheld and symptomatic treatment should be given as needed.

Sincerely yours,

FREDERICK S. HOWARD, M.D.

REFERENCES

1. Huggins, C., Stevens, R. E., Jr., and Hodges, C. V.: Studies in prostatic cancer, Arch. Surg., 43:209, 1941.

2. Tagnon, H. J., Schulman, P., Whitmore, W. F., and Leone, L. A.: Prostatic fibrinolysin, Am. J. Med., 15:875, 1953.

3. Whitmore, W. F., Randall, H. T., Pearson, O. H., and West, C. D.: Adrenalectomy in prostatic cancer, Geriatrics, 9:62, 1954.

4. Scott, W. W.: Carcinoma of the Prostate in Meredith Campbell's Urology, Saunders, 1954 (p. 1161).

5. Queries and minor notes, J.A.M.A., 163:704, Feb. 23, 1957.

6. Valk, W., and Owens, R. H.: Effect of cortisone on patients with carcinoma of the prostate, J. Urol., 71:219, 1954.

Congenital Absence of the Gallbladder

IN CALIFORNIA MEDICINE for December 1956, Monroe and Ragen report a case of congenital absence of the gallbladder and review of the literature.

Kaufman, in his three-volume work on pathology, translated by Stanley Reiman of Philadelphia and published about 1929, states that congenital absence of the gallbladder is rare and that he had personally seen two cases.

I have seen two such cases, both in women. One case I saw at operation for a supposedly nonfunctioning gallbladder, the other at autopsy. That is an incidence of one case in more than 16,000 autopsies performed by me. I have forgotten where, but many years ago I read that the incidence is about 1:14,000.

To my personal knowledge, the late Dr. A. F. Wagner, chief autopsy surgeon to the Coroner, Los Angeles County, performed about 13,000 autopsies during the years 1929 to 1937 and found no case of congenital absence of the gallbladder during that period.

One cannot deny what the literature cited by Monroe and Ragen says, but I cannot believe that it presents the true picture. The over-all incidence cited is 1:1,070. The range is from 1:5,000 to 1:270. Many busy pathologists have never seen a case. I can think of few things which are so uniformly ignored in textbooks on anatomy and pathology as congenital absence of the gallbladder. When mentioned at all it is merely mentioned in passing.

It is high time that anatomists and pathologists report such cases and give incidence. In this connection the fact that one person does 1,000 autopsies and finds two such cases means nothing. He may perform twenty thousand more without seeing another. Large series by very busy services over a period of years should give some reliable figures.

How many surgeons have ever seen such a case? If such cases are as frequent as the figures cited by Monroe and Ragen would indicate, hospital records should be full of them.

JOHN H. SCHAEFER, M.D.

Los Angeles

Dr. Schaefer's letter was referred to the senior author of the case report in question, who replied:

In reviewing the literature, it occurred to us that the apparent incidence of congenital absence of the gallbladder seemed quite high, on the basis of reported cases. However, we could report only what we found since there seemed to be no statistical data to support our impression. I fully agree with Dr. Schaefer that to arrive at the incidence of a rare anomaly, it is necessary to have an extremely large statistical sample, and the rarer the lesion the greater the need for a large sample.

In conclusion, then, we agree with Dr. Schaefer that the real incidence of congenital absence of the gallbladder is probably considerably less than 1:1,070 but would like to emphasize that we were merely reporting the literature as we found it. The senior author plans to carry out a more embracing statistical study of this anomaly.

STANLEY EDWIN MONROE, M.D.

CALIFORNIA MEDICAL ASSOCIATION

announces the

1957 ANNUAL SESSION

AMBASSADOR HOTEL, LOS ANGELES

APRIL 28 – MAY 1, 1957

Registration daily, 9 a.m. to 5 p.m. • No Registration Fee

Banquet honoring the President

TUESDAY, APRIL 30, 1957

House of Delegates

will meet

SUNDAY, APRIL 28, and WEDNESDAY, MAY 1, 1957

In The Ambassador Hotel

- *Members should bring membership cards for identification.*
- Non-member physicians will be registered upon proper identification.
- Nurses, technicians, medical students and office assistants will be registered upon identification from employing physicians, medical schools, etc.
- Pharmacist mates and other military personnel of like grade will be admitted upon presentation of a letter requesting their admittance, written by their commanding officer.
- Dentists (D.D.S.), doctors of veterinary medicine (D.V.M.), dietitians and allied public health personnel will be registered upon proper identification.

4 DAYS OF SCIENTIFIC MEETINGS • TECHNICAL EXHIBITS

SCIENTIFIC EXHIBITS • MEDICAL MOTION PICTURES

In Memoriam

ANDERTON, HERBERT SETH. Died in San Diego, February 15, 1957, aged 68. Graduate of the University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1910. Licensed in California in 1912. Doctor Anderton was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✤

BESSER. RUDOLPH W. Died in Burbank, February 10, 1957, aged 49, of aneurysm of the aorta. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1937. Licensed in California in 1938. Doctor Besser was a member of the Los Angeles County Medical Association.

✤

BONTHIUS, ANDREW. Died February 24, 1957, aged 76. Graduate of Northwestern University Medical School, Chicago, 1909. Licensed in California in 1914. Doctor Bonthius was a member of the Los Angeles County Medical Association.

✤

COLE, GEORGE MAYNARD. Died in Brawley, February 22, 1957, aged 54, of heart disease. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1943. Licensed in California in 1943. Doctor Cole was a member of the Imperial County Medical Society.

✤

HAMILTON, ROBERT L. Died recently, aged 52. Graduate of the University of Tennessee College of Medicine, Memphis, 1929. Licensed in California in 1929. Doctor Hamilton was a member of the Yuba-Sutter-Colusa County Medical Society.

✤

HARTSOUGH, CHRISTOPHER WILLIAM. Died in Durham, North Carolina, October 23, 1956, aged 48, of aortic stenosis. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1935. Licensed in California in 1935. Doctor Hartsough was an associate member of the San Diego County Medical Society.

✤

HAWKINS, JOSEPH OREY. Died in San Rafael, February 22, 1957, aged 51. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1929. Licensed in California in 1929. Doctor Hawkins was a member of the Marin County Medical Society.

HEARD, WESLEY ROBERT. Died in Monterey, March 1, 1957, aged 58. Graduate of the University of Western Ontario Faculty of Medicine, London, Ontario, Canada, 1924. Licensed in California in 1925. Doctor Heard was a member of the Monterey County Medical Society.

✤

MCINTURFF, DAVID NATHANIEL. Died in Sunnyvale, February 14, 1957, aged 54. Graduate of the University of Oregon Medical School, Portland, 1930. Licensed in California in 1937. Doctor McInturff was a member of the Santa Clara County Medical Society.

✤

MASON, CLIFFORD VERNE. Died in Santa Cruz, September 27, 1956, aged 63, of myocardial infarction. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1926. Licensed in California in 1926. Doctor Mason was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✤

RANKER, EMERY R. Died in Oakland, February 4, 1957, aged 60, of coronary thrombosis. Graduate of Northwestern University Medical School, Chicago, 1933. Licensed in California in 1933. Doctor Ranker was a member of the Alameda-Contra Costa Medical Association.

✤

SCHMITT, LIONEL SAMUEL. Died in San Francisco February 5, 1957, aged 80. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1901. Licensed in California in 1901. Doctor Schmitt was a member of the San Francisco Medical Society.

✤

SUTHERLIN, CECIL GLENN. Died in San Diego, February 22, 1957, aged 69. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1913. Licensed in California in 1922. Doctor Sutherlin was a retired member of the Los Angeles County Medical Association and the California Medical Association and an associate member of the American Medical Association.

✤

WOOLFORD, JOSEPH SIDNEY. Died January 30, 1957, aged 59. Graduate of the University of Louisville School of Medicine, Louisville, Kentucky, 1927. Licensed in California in 1928. Doctor Woolford was a member of the Humboldt County Medical Society.

WOMAN'S AUXILIARY
TO THE CALIFORNIA MEDICAL ASSOCIATION

Dear Doctor:

Another year is coming to a close for your Woman's Auxiliary and this will be my last visit with you. I hope you have followed us through these pages and have come to know us for our various activities in behalf of the medical profession.

We are proud of our achievements in the field of nurse recruitment and have many newly sponsored future nurses' clubs among the young girls in the junior high schools. This is one phase of our work to which we are very dedicated because it means so much, both to you and to the communities in which we live.

The funds are coming in very well for the American Medical Education Foundation and we are sure that we will receive notice of our generosity at the national convention.

We have made rapid strides in the extension of interest in *Today's Health* this year. Los Angeles County received a prize for having secured the most subscriptions in Class 4 at Christmas time. We are distinctly proud of this fact.

We are actively engaged at present in carrying forth a campaign of contacting our state legislators in regard to the cancer bill, in which you doctors are so vitally interested.

So in each field pertinent to medicine your auxiliary has been active and has had the pride of achievement.

I recently have returned from my official visit to many of our northern counties and find a great alertness and interest in every one of the counties. This leads me to believe that there exists a relationship between the county medical societies and the auxiliaries which is very gratifying because of the enthusiasm. Perhaps our little visits each month have reached you after all, and perhaps you have come to feel that you have a right hand in the auxiliary upon which you can always count to deal an effective blow in your behalf.

A new president will very soon be in charge of your auxiliary and I hope you will extend to her all of the courtesy, understanding and cooperation which, through your county medical societies, you have extended to me this year.

It has been a distinct pleasure to serve you as president of the Woman's Auxiliary to the California Medical Association and I am proud indeed of each of our component county auxiliaries and the pride they are taking in this, their dedicated field of service.

Cordially yours,

MRS. PAUL C. BLAISDELL, *President*
Woman's Auxiliary to the
California Medical Association

Twenty-seventh Annual Convention

WOMAN'S AUXILIARY
TO THE
CALIFORNIA MEDICAL ASSOCIATION
Los Angeles, April 28 to 30
HEADQUARTERS . . . . . AMBASSADOR HOTEL

NEWS & NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

Dr. Sydney S. Gellis, professor of pediatrics and chairman of the department of pediatrics at Boston University School of Medicine, will lecture during the sixth annual **Clifford Sweet Lectureship** at Children's Hospital of the East Bay, Oakland, scheduled for June 7 and 8. His principal lecture, entitled "Iatrogenic Diseases," will be given at 6 p.m. in connection with the annual opening night banquet.

Further information may be obtained from Children's Hospital of the East Bay, 5105 Dover Street, Oakland 9, OLympic 2-1143.

LOS ANGELES

The Los Angeles County Heart Association is receiving applications for **research grants in the field of cardiovascular diseases** for 1957-1958. Any investigator is eligible to make application for a grant. Applications must be received by the Heart Association by May 1.

Grants will be given priority as follows: First, research into the causes and means of prevention of heart disease; second, studies of methods of diagnosis of individual cases of heart disease.

Detailed information may be obtained by writing to the Los Angeles County Heart Association, 660 South Western Avenue, Los Angeles 5, or by calling DUnkirk 5-4231. Grants will be announced by June 1, 1957.

* * *

The **Los Angeles County Women's Medical Society** has invited women physicians and their guests to attend a joint meeting of that organization and the Los Angeles County Women Lawyers to be held at the Chapman Park Hotel, 615 South Alexandria, Los Angeles, in the Gold Room on May 1 at 7:00 p.m.

Dinner will be served. The price of dinner will be approximately $4.75, the announcement said.

* * *

The **California Medical Association golf tournament** will be held this year at the Montebello Country Club on Monday, April 29, 1957. Golfers may tee off between 10 a.m. and 1 p.m. Foursomes will be made up at the first tee by the starter. The usual four flights will be segregated according to handicaps. Those with handicaps above 25 will compete with the "compleat duffers." The course is reported to be in excellent condition.

A social hour and dinner to award prizes to the winners will take place in the dining room of the club beginning at 6 p.m. Dinner should be completed by 8:30 p.m. Any wives who wish may be served dinner at the club that evening.

For out-of-towners: The Montebello Club is easily reached from any downtown hotel by Hollywood Freeway east to Ramona Freeway, thence east to Garfield Avenue turnoff south. Garfield Avenue extends to the Montebello Country Club.

SAN FRANCISCO

The fourth annual **medical symposia** given by the medical service of Fort Miley Hospital, San Francisco, in cooperation with Stanford University and University of California medical schools, has been announced by the **San Francisco Academy of General Practice.** Six in all, the symposia will be held each Tuesday evening, April 16 to May 21, from 8 to 10 o'clock in the Fort Miley Hospital auditorium. The program:

April 16: A Symposium on Endocrinology—Peter Forsham, M.D., Felix Kolb, M.D., and Max Rukes, M.D.

April 23: Myocardial Infarction and Coronary Artery Disease—John Sampson, M.D., Robert L. Smith, Jr., M.D., Maurice Sokolow, M.D., and Arthur Selzer, M.D.

April 30: The Diagnosis and Treatment of the Comatose Patient—Clayton D. Mote, M.D., Paul Sanazaro, M.D., Robert H. Alway, M.D., and Frederick A. Fender, M.D.

May 7: Fever of Unknown Origin—Arthur L. Bloomfield, M.D., Henry Brainerd, M.D., and H. Corwin Hinshaw, M.D.

May 14: Symposium on Gastrointestinal Disease—Claude Callaway, M.D., John Carbone, M.D., Hugo Moeller, M.D., and Louis Brizzolara, M.D.

May 21: Symposium on Lymphoma and Cancer—Byron E. Hall, M.D., L. Henry Garland, M.D., and Leonard G. Dobson, M.D.

* * *

Dr. Robert H. Alway has been named acting dean of Stanford School of Medicine, effective at once, to replace Dr. Windsor C. Cutting, who resigned as dean in January but continued in the post until a successor could be found. Dr. Cutting will remain a member of the medical faculty.

Dr. Jay Ward Smith, associate dean, and Dr. Lyman M. Stowe, assistant dean, will continue to serve under the new acting dean.

A committee headed by Wallace Sterling, president of the university, has been appointed to select a permanent dean for the medical school. It includes Drs. Alway and Smith, Claude P. Callaway, William W. Greulich, Henry S. Kaplan, Robert R. Sears, William C. Steere, and Dwight L. Wilbur.

* * *

Two members of the faculties of medical schools in California have been awarded American Cyanamid Co. **grants in support of research.** They are: Dr. Alexander N. Contopoulos, Department of Anatomy, University of California, Berkeley, who received a one-year grant, and Dr. Robert J. Roantree, Department of Microbiology, Stanford University, a three-year grant.

"The basic purpose of the grants," the announcement said, is to help assure to schools and universities adequate funds to encourage medical men of stature to continue in teaching and research posts." The amounts of the grants were not announced.

SANTA BARBARA

The 1957 meeting of the **Western Orthopedic Association** is to be held in Santa Barbara, October 20 to 24. Officers for 1957 are: Samuel S. Mathews, M.D., Los Angeles, president; Richard McGovney, M.D., Santa Barbara, vice-president; and Walter Scott, M.D., Los Angeles, secretary-treasurer.

POSTGRADUATE

EDUCATION NOTICES

THIS BULLETIN of the dates of postgraduate education programs and the meetings of various medical organizations in California is supplied by the Committee on Postgraduate Activities of the California Medical Association. In order that they may be listed here, please send communications relating to your future medical or surgical programs to: Mrs. Margaret H. Griffith, Director, Postgraduate Activities, California Medical Association, 417 South Hill Street, Los Angeles 13.

UNIVERSITY OF CALIFORNIA AT LOS ANGELES

Inhalation Therapy. Wednesday, April 24. Six hours. Fee: $17.50.

Dissection of Extremities. Mondays, April 29 through June 10. Seventeen hours. Fee: $125.00.

Problems of the Newborn. June 13 to 15. Fifteen hours. Fee: $60.00.

Techniques of Hypnosis. Monday, Tuesday and Wednesday morning, June 24, 25 and 26. Fifteen hours. Fee: $60.00.

Advanced Techniques and Application of Hypnosis. Wednesday afternoon, Thursday and Friday, June 26, 27, 28. Fifteen hours. Fee: $100.00.

Contact: Thomas H. Sternberg, M.D., Assistant Dean for Postgraduate Medical Education, U.C.L.A., Los Angeles 24. BRadshaw 2-8911, Ext. 202.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Fundamental Principles of Radioactivity and the Diagnostic and Therapeutic Uses of Radioisotopes. Two or three month course limited to one enrollee per month. Tuition: $250.00 per month.

Medical Ophthalmology and Ophthalmoscopy. Thursday and Friday, May 16 and 17. Fourteen hours. Fee: $60.00.

Arthritis and Rheumatic Diseases. Thursday and Friday, May 16 and 17.*

Ear, Nose, Throat, Clinics and Seminars. Friday and Saturday, May 24 and 25.*

Pediatrics. June 11 to 14.*

Contact: Seymour M. Farber, M.D., Head, Postgraduate Instruction, Office of Medical Extension, University of California Medical Center, San Francisco 22. MOntrose 4-3600, Ext. 665.

STANFORD UNIVERSITY SCHOOL OF MEDICINE

Morning Clinical Conferences, each Monday, Room 515. *Contact:* D. H. Pischel, M.D., Professor, Division of Ophthalmology, Stanford University School of Medicine, 2398 Sacramento St., San Francisco 15.

*Hours and Fees to be announced.

UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES

Home Course in Electrocardiography. Physicians may register at any time and receive all 52 issues. Fifty-two weeks. Fee: $100.00.

Cardiac Resuscitation. Sponsored by the Los Angeles County Heart Association each Wednesday throughout the year, 4 to 6 p.m. Residents admitted without fee. Tuition for all other physicians: $30.00. (Each session all-inclusive.)

Contact: Phil R. Manning, M.D., Director, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 33. CApital 5-1511.

COLLEGE OF MEDICAL EVANGELISTS

Thoracic Surgery. Wednesdays, April 24 through May 15, 1957. Eight hours.

Contact: Chairman, Section on Graduate and Postgraduate Medicine, College of Medical Evangelists, 1720 Brooklyn Ave., Los Angeles 33. ANgelus 9-9131, Ext. 205.

CALIFORNIA MEDICAL ASSOCIATION POSTGRADUATE COURSES

AUDIO DIGEST FOUNDATION, a nonprofit subsidiary of the C.M.A., now offers (on a subscription basis) a series of hour-long tape recordings designed to keep the physician abreast of current happenings in his particular field. Composed of practice-useful abstracts from 600 leading journals, with short lectures and editorial comments from prominent physicians, Audio Digest offers programs covering general practice, surgery, internal medicine, obstetrics and gynecology, and pediatrics.

Contact: Claron L. Oakley, editor, 1919 Wilshire Blvd., Los Angeles 57.

POSTGRADUATE INSTITUTES, 1957

SACRAMENTO VALLEY COUNTIES in cooperation with College of Medical Evangelists, June 19 to 21, 1957, Tahoe Tavern, Lake Tahoe. Chairman: C. M. Blumenfeld, M.D., 4700 Parkridge Road, Sacramento.

Contact: The chairman listed above, or Mrs. Margaret H. Griffith, Director, Postgraduate Activities, California Medical Association, 417 So. Hill Street, Los Angeles 13. Madison 6-0683.

Medical Dates Bulletin

APRIL MEETINGS

SAN FRANCISCO HEART ASSOCIATION Nurses Institute on the Care of the Cardiac Patient, April 17 and 18, 8:30 a.m. to 5 p.m., San Francisco. *Contact:* Mr. Lawrence Kramer, Executive Director, San Francisco Heart Association, 604 Mission Street, San Francisco, or telephone: YUkon 2-5753.

CANCER COMMISSION, CALIFORNIA MEDICAL ASSOCIATION, Cancer Conference for San Luis Obispo County Medical Society, April 20.§

§*Contact:* Walter E. Batchelder, M.D., Medical Director, Cancer Commission, Suite 816, 450 Sutter St., San Francisco.

‡*Contact:* Major Max E. Knickerbocker, MSC, Chief of Education and Training Branch, Letterman Army Hospital, San Francisco.

LETTERMAN ARMY HOSPITAL "Oral Surgery," 8 a.m. to 4:30 p.m., April 22 to 26.‡

ST. MARY'S HOSPITAL, San Francisco, Annual Staff Day. Hospital Auditorium, April 24, 9 a.m. to 4 p.m. Guest speakers: Alexander Brunschwig, M.D., New York; James W. Colbert, M.D., St. Louis; Edward G. Biglieri, M.D., Maryland. Memorial Dinner at St. Francis Hotel, 6 p.m. Fee: $20.00, includes lunch and dinner. *Contact:* Frank A. Solomon, Jr., M.D., St. Mary's Hospital.

CANCER COMMISSION, CALIFORNIA MEDICAL ASSOCIATION, Cancer Conference for Merced County Medical Society, April 25.§

CALIFORNIA CHAPTER, AMERICAN COLLEGE OF CHEST PHYSICIANS Annual Meeting, Ambassador Hotel, Los Angeles, Saturday, April 27. *Contact:* Marvin Harris, M.D., president, 6317 Wilshire Blvd., Los Angeles.

CALIFORNIA MEDICAL ASSOCIATION Annual Meeting, Ambassador Hotel, Los Angeles, April 28 to May 1. *Contact:* John Hunton, executive secretary, 450 Sutter St., San Francisco 8, or Ed Clancy, director of Public Relations, 417 S. Hill St., Los Angeles 13.

MAY MEETINGS

CALIFORNIA CONFERENCE OF LOCAL HEALTH OFFICERS. Auditorium, State Building, 217 West First Street, Los Angeles, May 2 and 3. *Contact:* Donald G. Davy, M.D., State Dept. of Public Health, 2151 Berkeley Way, Berkeley.

CANCER COMMISSION, CALIFORNIA MEDICAL ASSOCIATION, Cancer Conference for Napa County Medical Society, May 8.§

NEVADA CHAPTER, AMERICAN ACADEMY OF GENERAL PRACTICE Annual State Meeting, Riverside Hotel, Reno, Nevada, May 10 to 11. *Contact:* Robert F. Biglin, M.D., chairman, 1338 S. Virginia St., Reno.

CALIFORNIA HEART ASSOCIATION Annual Meeting Lafayette Hotel, San Diego, May 17, 18, and 19. *Contact:* J. Keith Thwaites, executive director, California Heart Association, 1428 Bush Street, San Francisco.

WESTERN BRANCH, AMERICAN PUBLIC HEALTH ASSOCIATION annual meeting, Lafayette Hotel, Long Beach, May 29 and June 1. *Contact:* Mrs. L. Amy Darter, Secretary-Treasurer, State Dept. Public Health, 2151 Berkeley Way, Berkeley.

JUNE MEETINGS

CHILDREN'S HOSPITAL OF THE EAST BAY Pediatric Seminar and Clifford Sweet Lectures, June 7 to 8. Guest lecturer: Sydney S. Gellis, M.D., Boston. *Contact:* James Dennis, M.D., medical director, 5105 Dover St., Oakland 9.

STATE BOARD OF MEDICAL EXAMINERS Oral Examination, San Francisco, June 15.*

IDAHO STATE MEDICAL ASSOCIATION 65th Annual Meeting, Sun Valley, June 16 to 19. *Contact:* Mr. Armand L. Bird, executive secretary, 364 Sonna Bldg., Boise, Idaho.

STATE BOARD OF MEDICAL EXAMINERS Written Examination, San Francisco, June 17 to 20.

WYOMING STATE MEDICAL SOCIETY ROCKY MOUNTAIN MEDICAL CONFERENCE Annual Joint Meeting, Jackson Lake Lodge, Moran, Wyoming, June 16 to 19. *Contact:* H. L. Harvey, M.D., Casper, Wyoming.

SUMMER AND FALL MEETINGS, 1957

COLORADO DIVISION, CANCER SOCIETY ROCKY MOUNTAIN Cancer Conference, 9 a.m., July 10 and 11, Shirley-Savoy Hotel, Denver. *Contact:* John S. Bouslog, M.D., Chairman, 835 Republic Bldg., Denver 2.

STATE BOARD OF MEDICAL EXAMINERS Oral Examination, Los Angeles, August 17.*

STATE BOARD OF MEDICAL EXAMINERS Written Examination, Los Angeles, August 19 to 22.

UTAH STATE MEDICAL ASSOCIATION Annual Scientific Session, September 5 to 7, Hotel Utah, Salt Lake City, Utah. *Contact:* Harold Bowman, 42 South Fifth Street, Salt Lake City.

SAINT JOHN'S HOSPITAL Annual Postgraduate Assembly, September 12 to 14, Saint John's Hospital, Santa Monica. *Contact:* John C. Eagan, M.D., director, Postgraduate Assembly, 22nd Street at Santa Monica Blvd., Santa Monica.

WASHINGTON STATE MEDICAL ASSOCIATION Annual Meeting, Olympic Hotel, Seattle, Washington, September 15 to 18. *Contact:* Mr. Ralph W. Neill, executive secretary, 1309 Seventh Ave., Seattle, Washington.

SAN DIEGO COUNTY GENERAL HOSPITAL 11th Annual Postgraduate Assembly, September 18 to 19. Reception for all registrants, 5:00 to 7:00 p.m., September 18. *Contact:* Haddon A. Peck, Jr., M.D., 525 Hawthorne St., San Diego.

NEVADA STATE MEDICAL ASSOCIATION Annual Meeting, Las Vegas, September 25 to 28. *Contact:* Nelson B. Neff, executive secretary, P. O. Box 188, Reno.

SAN FRANCISCO HEART ASSOCIATION 28th Annual Postgraduate Symposium on Heart Disease, October 2 to 4, St. Francis Hotel, San Francisco. *Contact:* Lawrence I. Kramer, Jr., executive director, 604 Mission St., San Francisco.

FIRST WESTERN INDUSTRIAL HEALTH CONFERENCE, Biltmore Hotel, Los Angeles. October 4 to 6. *Contact:* E. J. Zaik, M.D., secretary, Western Industrial Medical Association, 740 South Olive Street, Los Angeles 14.

SAN DIEGO COUNTY HEART ASSOCIATION Seventh Annual Professional Symposium on Heart Disease. U. S. Naval Hospital, San Diego, October 8. *Contact:* O. Martin Avison, executive director, San Diego County Heart Association, 1651 Fourth Ave., San Diego.

LOS ANGELES COUNTY HEART ASSOCIATION 27th Annual Symposium on Heart Disease, Wilshire-Ebell Theatre, 4401 W. Eighth St., Los Angeles, October 9-10. *Contact:* Walter S. Thompson, Jr., M.D., chairman, 660 S. Western Ave., Los Angeles.

CALIFORNIA SOCIETY OF INTERNAL MEDICINE Annual Meeting, October 25 to 27, El Mirador, Palm Springs. *Contact:* Mrs. Mildred B. Coleman, assistant secretary, 350 Post St., San Francisco 8.

CALIFORNIA ACADEMY OF GENERAL PRACTICE Ninth Annual Scientific Assembly, November 3 to 6, Hotel Statler, Los Angeles. *Contact:* William W. Rogers, executive secretary, 461 Market Street, San Francisco.

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*NOTE: In regard to the dates of oral examinations, applicants are requested *NOT* to arrange to come to an oral examination until they receive a notice of the action of the Credentials Committee advising them of the time and place to appear.

INFORMATION

A Way to Gauge Hospital Needs

ONE OF THE MAJOR DEMANDS upon the pocketbooks of the American people is the cost of illness and maintaining health, involving expenditures amounting to about twenty billion dollars a year. Of this amount, five and a half billion was spent in 1955 to cover the operating expenses of hospitals in the United States.

It is not generally realized, even in the face of such expenditure, that the operation and maintenance of the nation's hospitals constitute one of the largest of U. S. industries. In 1955, for example, the country's hospitals employed one and a third million full-time employees, and represented a twelve billion dollar investment in facilities and equipment.

In view of our rising national economy and population, demands upon hospital capacity are increasing along with the cost of providing for present and future needs. Consequently, various lay and professional groups and organizations responsible for the direction, management, and financing of the country's hospitals are becoming more and more interested in achieving greater efficiency in hospital administration and operation, maximum utilization of hospital facilities and services, and sound long-range planning. As in the case of other complex, large-scale, U. S. industries, however, such objectives require application of a scientific research approach to the various aspects and operations involved in the provision of hospital services today and tomorrow.

Until recently, the necessary information was available only through consultant opinions, from academic studies, from expert committees concerned with special phases or problems, or from special commissions created for specific tasks. The 15 schools of hospital administration in the United States concentrate on training personnel for the important job of directing such institutions. The Johns Hopkins Hospital recently established an operations research group to survey its own needs. Yale University, the Massachusetts Institute of Technology, and a few other institutions are conducting research regarding hospital operation.

At present, few organizations are interested in, and adequately staffed and available for the conduct on a broad and varied scale of the urgently needed studies and investigations of the specialized problems of hospitals and other organizations in the health field.

To help meet this need, the Stanford Research Institute's Health Economics Unit—probably the first group specifically concerned with applying the scientific research approach to the interrelated aspects of health administration—is conducting studies on several aspects of the health field. These include a variety of problems such as the determination of future facility needs, the development of sound financial practices, the utilization of modern techniques such as data-processing and automation, and the most productive allocation of resources.

THE OAHU HOSPITAL STUDY

A recently completed study of the hospital facility needs of the Hawaiian island of Oahu, prepared for the Public Health Committee, Honolulu Chamber of Commerce, illustrates the multifaceted character of hospital administration problems. It required the joint effort of economists, area planners, physicians, and operations research analysts to gather, analyze, and interpret the data and information necessary to obtain the desired answers.

The study considered the hospital facilities of Oahu as a whole in determining present capacity and future requirements to meet the needs of the entire civilian community. It was based on the major premises that the Oahu hospital goal was to provide adequate medical care to the public at minimum social and economic cost; that a patient on Oahu could be admitted to any vacant civilian hospital bed in any Oahu hospital providing the type of service required by his condition; and that the provision of hospital facilities is, in essence, paying an insurance "premium" to minimize the risk of future bed overloads.

DETERMINING HOSPITAL BED NEEDS—A NEW METHOD

A particularly important outcome of this study was the development of a new method for projecting hospital bed needs, stemming from the realization that absolute protection against hospital overload is not possible, regardless of the amount of bed capacity. From this premise, the concept of determining necessary hospital bed capacity in terms of maximum, practicable "insurance" against overload was established. For this study, a "bed" represented the entire hospital complex—staff, operating rooms, pharmacies, kitchens, and other supporting facilities —needed to care for the occupying patient.

The method of determining the "risk"—the likelihood of the bed load exceeding a given number during a future period—is based upon the establish-

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ment of probability data similar to life tables and other actuarial data employed in the calculation of insurance rates. The plotting of such data has provided a chart constituting a new "tool" to help any hospital administrator, and others interested, to determine hospital bed needs.

The SRI-developed chart shows the actual cumulative frequency distribution of the Oahu hospitals' pediatric patient case load for 1955 and parallel lines reflecting projections of the case load for 1960 and 1965, appropriately weighted to allow for growth trends in Oahu child population and consequent hospital bed loads. These lines are plotted on logarithmic-probability scales and indicate the probability of the occurrence of a given caseload. Intersection of the parallel lines with the desired overload probability percentage indicates the number of beds required to provide a given degree of insurance against overload.

For initial use, a one-in-a-thousand chance of bed demand exceeding capacity on any given day was considered satisfactory for the Oahu situation. The number of beds needed in 1960 and 1965 to keep the chances of an overload to one in a thousand was then calculated.

Similar charts were prepared for each type of in-patient service provided by Oahu hospitals. Comparison of the projected additional hospital bed need for each type of service indicates considerable difference in requirements and reflects the sensitivity of the method to the basic data employed.

This new method of projecting hospital bed needs has been received with considerable interest by hospital administrators. It is immediately applicable to almost any special or general short-term hospital in-patient service; it develops the desired data by utilizing the experience of the past as a basis for projecting to the future, assuming that hospital trends are normally evolutionary; it readily fits in with today's general methods, procedures, and records; and it avoids the rigidity imposed by applying national or statewide bed need averages to particular locales.

ECONOMIC ASPECTS OF OAHU HOSPITAL OPERATION

Since the provision of additional hospital bed capacity requires increased facilities and resulting increased capital and operating expenditures, the operating expenses and revenue sources of Oahu hospitals were analyzed in order to place the cost of construction in proper perspective compared with total hospital cost. The resulting data, encompassing various phases of hospital operation, indicated that the entire prorated cost of the Oahu hospital plant, including buildings and all facilities, was only 4 per cent of the annual hospital budget. Staff salaries, on the other hand, consumed two-thirds of the total expense.

It was concluded, therefore, that maximum effort should be made to determine areas where the expenditure of capital funds for new equipment and facilities could increase the productivity of personnel and to consider new systems, automation, or medical care plans contributing to more uniform and economic use of facilities and staff. Resulting economies, especially in connection with the labor content of hospital services, could compensate, in the long run, for the capital outlay.